EXHIBIT A

1

COMMONWEALTH OF MASSACHUSETTS

MIDDLESEX, SS.

SUPERIOR COURT
NO. 22-628

MICHAEL BUSH

Plaintiff

v.

The Wang Center for the Performing Arts, Inc.
d/b/a Boch Center

Defendant

FILED
IN THE OFFICE OF THE
CLERK OF COURTS
FOR THE COUNTY OF MIDDLESEX
JAN 31 2022
CLERK

VERIFIED COMPLAINT

Parties

1. The Plaintiff, Michael Bush, ("Bush") is a natural person who resides at 280 Lowell Street, Carlisle, Middlesex County, Massachusetts.

2. The Defendant, The Wang Center for the Performing Arts, Inc. ("Boch Center") is a nonprofit corporation organized under the laws of the Commonwealth of Massachusetts with a principal office located at 270 Tremont Street, Boston, Suffolk County, Massachusetts.

Jurisdiction and Venue

3. Jurisdiction is correct in the Superior Court because there is a reasonable likelihood that the recovery by the Plaintiff will be greater than $50,000.00. See M.G.L. Ch. 212, § 3 and Supreme Judicial Court Order regarding amount-in-controversy requirement under G.L. c. 218, § 19 and G.L. c. 212, § 3 effective January 1st, 2020.

4. Venue is correct because the Plaintiff resides within Middlesex County.

Factual Background to This Claim Asserted and Verified by Plaintiff, Michael Bush

5. Using the hyperlinks in the Boch Center's promotional email messages to Bush, on July 25th, 2021 Bush purchased tickets online to the Cirque Dreams Holidaze show to be held at the Boch Center Shubert Theatre on December 11, 2021.

6. On July 11th, 2021 Bush purchased tickets online to the Il Divo "For Once In My Life" Tour show to be held at the Boch Center Wang Theatre on September 3rd, 2021.

7. Nowhere in the Boch Center's promotional emails or the online purchase process was it disclosed to Bush that he would have to undergo "vaccination(s)", medical test(s) and/or wear a mask in order to attend the shows.

8. Had Boch Center disclosed such medical requirements to Bush prior to and/or during the purchase process, he would not have purchased the tickets.

9. Bush purchased the tickets with the intention to attend both shows with his wife. He looked forward to what he anticipated would be relaxing and fun experiences with his wife at those shows.

10. Subsequent to his ticket purchases, Bush received an email message informing him that the Il Divo show had been rescheduled to February 22nd, 2022.

11. On August 23rd, 2021 the United States Food and Drug Administration ("FDA") granted and announced formal approval/licensure to Pfizer's COMIRNATY COVID-19 mRNA "vaccine". (See Exhibit 1 enclosed.)

12. After the FDA's licensure of COMIRNATY, on August 23rd, 2021 Bush received an email message from Boch Center (enclosed as Exhibit 2 and hereinafter referred to as the

"policy") informing him that commencing September 14th, 2021 he and other guests at Boch Center's theatres' shows would have to wear mask(s) as well as show evidence of "COVID-19 vaccination" or show a negative COVID test result to attend show(s) for which Bush had previously purchased tickets.

13. Bush was shocked and dismayed by Boch Center's policy, which caused him to experience anxiety, sadness, and despair because he has a medical condition that prevents him from wearing a face mask and the policy led him to believe he would be barred from attending the shows for which he had purchased tickets on the basis of his disability. (See Bush's physician's letter enclosed as Exhibit 3.)

14. Boch Center wrongly used Boston Public Health Commission's Order Requiring Face Coverings In The City Of Boston dated August 20, 2021 as justification for its face mask policy. (See Exhibit 4 enclosed).

15. That Boston Public Health Commission Order stated that, "face coverings are not required for children under two years of age, anyone who has trouble breathing, anyone who is unconscious, incapacitated or otherwise unable to remove the mask without assistance, or anyone who due to disability is unable to wear a mask."

16. Boch Center's policy allowed for none of the exemptions the Boston Public Health Commission Order specified.

17. According to Boch Center's own policy, a show guest/invitee would be allowed entry even if they were coughing and feverish and tested positive for COVID-19/SARS-CoV-2 upon arrival as long as the guest showed proof of "COVID-19 vaccination" and wore a mask.

18. According to Boch Center's own policy, a show guest/invitee would be allowed entry even if they tested positive for Ebola virus and displayed multiple symptoms of Ebola infection as long as the guest showed proof of "COVID-19 vaccination" and wore a mask.

19. According to Boch Center's own policy, a show guest would be allowed entry even if they tested positive for measles, showed measles rash, and displayed multiple symptoms of measles infection as long as the guest showed proof of "COVID-19 vaccination" and wore a mask.

20. Boch Center's policy makes no accommodation for naturally-acquired immunity to SARS-CoV-2/COVID-19 such as test results showing antibodies or T cells in lieu of COVID virus testing and/or proof of vaccination.

21. Studies have shown that naturally-acquired immunity to SARS-CoV-2/COVID-19 confers resistance to re-infection superior to and protection from COVID-19 disease lasting longer than that conferred by "COVID-19 vaccinations". See https://brownstone.org/articles/how-likely-is-reinfection-following-covid-recovery/

22. Bush has naturally-acquired, documented immunity to COVID-19.

23. Boch Center's policy unfairly discriminates against Bush for his naturally-acquired immunity by requiring him to show and/or pay for a negative COVID test that the Boch Center does not require of show guests/invitees who show evidence of COVID-19 "vaccination".

24. Pfizer's COMIRNATY is the only "COVID-19 vaccine" product to have received formal approval/licensure by the FDA so far.

25. On and since August 23rd, 2021, there has been no COMIRNATY product available in the U.S.A. (See page 19 of Exhibit 5 enclosed.)

26. The only "COVID-19 vaccines" available in the U.S.A. have been granted emergency use authorization ("EUA") by the FDA.

27. Medical products granted EUAs by the FDA are only authorized for investigational/experimental usage.

28. By law, EUAs for other medical products must be withdrawn by the FDA if a medical product formally approved for that same purpose is available for use.

29. Boch Center's policy effectively requires customers to be "fully vaccinated" with a product authorized only for investigational/experimental usage and without formal approval/licensure by the FDA or to subject themselves to a COVID test authorized only for investigational/experimental use.

30. Boch Center's policy failed to disclose that the only "COVID-19 vaccines" available in the U.S.A. are not approved or licensed by the FDA.

31. Boch Center's policy requires all guests/customers to wear masks to purportedly "stop the spread" of COVID-19 without legal authority.

32. The FDA is the sole agency that regulates medical devices and products in the U.S.A.

33. The U.S. Centers for Disease Control and Prevention does not regulate medical devices or products.

34. The FDA has not approved any masks to stop the spread of COVID-19 or other viral respiratory infections.

35. The FDA has not granted an EUA to any masks to stop the spread of COVID-19 or other viral respiratory infections in a community setting such as a theater.

36. In its August 5th, 2020 letter (enclosed as Exhibit 6), the FDA granted an EUA for certain surgical masks, "limited to the use of the authorized surgical masks, for use in healthcare settings by HCP as PPE to provide a physical barrier to fluids and particulate materials to prevent HCP exposure to respiratory droplets and large particles during surgical mask shortages resulting from the COVID-19 pandemic."

37. In its August 5th, 2020 EUA letter, the FDA also stated that the labeling of the authorized surgical masks must:

- "State that surgical masks are not intended to provide protection against pathogenic biological airborne particulates and are not recommended for use in aerosol generating procedures and any clinical conditions where there is significant risk of infection through inhalation exposure; and
- Not include statements that would misrepresent the product or create an undue risk in light of the public health emergency. For example, the labeling must not include any express or implied claims for: (1) reuse, (2) antimicrobial or antiviral protection or related uses, (3) infection prevention, infection reduction, or related uses, or (4) viral filtration efficiency."

38. Some COVID-19 tests may have EUA from the FDA but to date none have been approved or licensed.

39. Title 21 U.S.C. § 360bbb-3(e)(1)(A)(ii)(I-III) of the Federal Food, Drug, and Cosmetic Act states of EUA products that individuals to whom the product is administered must be informed:

- that the Secretary has authorized the emergency use of the product;

- of the significant known and potential benefits and risks of such use, and of the extent to which such benefits and risks are unknown; and
- of the option to accept or refuse administration of the product, of the consequences, if any, of refusing administration of the product, and of the alternatives to the product that are available and of their benefits and risks.

40. Boch Center has failed to inform guests/customers of the above facts about the COVID-19 tests it offers to conduct for them on site.

41. Boch Center's policy is deceptive in that it implies wearing face masks that are not approved by the FDA for stopping the spread of COVID-19 will stop the spread of COVID-19.

42. Prior to Boch Center issuing its policy, the body of evidence was already present refuting the efficacy of face masks for stopping the spread of SARS-CoV-2/COVID-19. See Exhibit 7 with its stated conclusion that, "The use of cloth facemasks in community settings has become an accepted public policy response to decrease disease transmission during the COVID-19 pandemic. Yet evidence of facemask efficacy is based primarily on observational studies that are subject to confounding and on mechanistic studies that rely on surrogate endpoints (such as droplet dispersion) as proxies for disease transmission. The available clinical evidence of facemask efficacy is of low quality and the best available clinical evidence has mostly failed to show efficacy, with fourteen of sixteen identified randomized controlled trials comparing face masks to no mask controls failing to find statistically significant benefit in the intent-to-treat populations." Though the review was dated November 2021, all or virtually all of the studies it reviews were

published before Boch Center issued its policy claiming face masks are required of guests to "stop the spread" of COVID-19.

43. Prior to Boch Center issuing its policy, it was publicly known and well-documented that the "COVID-19 vaccines" in use in the U.S.A. do not stop infection or transmission of the SARS-CoV-2 virus. See https://www.cnbc.com/2021/07/30/cdc-study-shows-74percent-of-people-infected-in-massachusetts-covid-outbreak-were-fully-vaccinated.html and https://www.medrxiv.org/content/10.1101/2021.07.31.21261387v4 and https://link.springer.com/article/10.1007/s10654-021-00808-7

44. Prior to Boch Center issuing its policy, it was well-documented that wearing face masks has a range of physical and psychological harms. (See Exhibit 8 enclosed.)

45. Boch Center has negligently failed to disclose to guests/customers the known harms of wearing face masks.

46. Representing Bush, on September 21, 2021 attorney Richard C. Chambers, Jr. ("attorney Chambers") delivered via the U.S. Postal Service to Boch Center Bush's M.G.L. Ch. 93A 30 Day Notice and Demand letter (enclosed as Exhibit 9).

47. Boch Center, via attorney Bruce Falby of DLA Piper LLP, sent Bush a response letter dated September 27, 2021 (enclosed as Exhibit 10).

48. In its response letter, Boch Center cited no medical or legal references.

49. In its response letter, Boch Center threatened to seek sanctions per an unspecified "Rule 11" if Bush asserted his constitutionally-protected legal rights via litigation.

50. On behalf of Bush, attorney Chambers had the U.S. Postal Service deliver via certified mail to the Defendant's counsel on November 17th, 2021 a reply letter dated November

15th, 2021 again requesting a fair resolution of the Boch Center's violations of Bush's civil and consumer rights (enclosed as Exhibit 11).

51. To this date Boch Center has failed to respond to Bush's letter dated November 15th, 2021.

52. To this date Boch Center has failed to acknowledge or address the issue that face masks are medically inappropriate for Bush despite having been informed of that in Bush's M.G.L. Ch. 93A Notice and Demand letter.

53. Despite Bush having communicated that he did not want a refund and to the contrary wanted his legal rights honored and the Boch Center's policy brought into conformance with applicable laws, on or about November 23rd, 2021 Bush was shocked and dismayed to learn that Boch Center unilaterally without authorization took Bush's tickets to the Cirque Dreams Holidaze show away and issued Bush a refund of his purchase price of $244.30.

54. Boch Center failed to communicate to Bush that Boch Center took his Cirque Dreams Holidaze show tickets away.

55. Boch Center failed to communicate to Bush that it issued him a refund or why it had done so without his permission.

56. The fact that Boch Center took Bush's Cirque Dreams Holidaze show tickets away against his wishes caused him to experience severe anxiety, sadness, humiliation, and despair.

57. On December 2, 2021 Bush was shocked and dismayed to receive an email message titled "Subject: Important Safety Information For Cirque Dreams Holidaze" from Boch Center. (Enclosed as Exhibit 12).

58. The December 2, 2021 email message caused Bush to suffer further anxiety, sadness, humiliation, and despair.

59. Boch Center has never alleged that Bush is a direct threat.

60. Boch Center has never alleged that Bush is a contagious carrier of SARS-Cov-2/COVID-19.

Additional Factual Background as Context

61. The virus associated with the infectious disease COVID-19—SARS-CoV-2—mutates readily, is airborne and highly transmissible, and has non-human animal reservoirs.

62. Eminent epidemiologist and professor of medicine at Stanford University Dr. Jay Bhattacharya and professor of economics at George Mason University Donald. J. Boudreaux explained in an August 2021 article published in the Wall Street Journal that no degree of oppressive measures or violation of civil liberties can eradicate or contain COVID-19. (See Exhibit 13 enclosed.)

63. Furthermore, they pointed out what has been self-evident to anyone willing to acknowledge the obvious: attempting to eliminate this germ and infectious disease which cannot be contained or eliminated without regard for civil liberties and other aspects of public health is both futile and harmful.

64. The Boch Center's policy makes the unverified claim that it is intended to "stop the spread" of COVID-19.

65. As stopping the spread of COVID-19 is impossible, the policy's claim is deceptive.

66. Boch Center could have used alternative measures to mitigate the spread of pathogenic germs in its facilities without violating civil or consumer rights, such as ventilation and air treatment technologies.

67. According to the Massachusetts Department of Public Health's data for the 7 day period ending December 25th, 2021, there were 20, 247 new COVID-19 cases amongst "fully vaccinated" residents, constituting 44% of new cases in that time period.

68. On December 20, 2021, Boston MA Mayor Michelle Wu announced that starting January 15, 2022 people over the age of 12 would be required to show proof of COVID-19 vaccination for entry to certain public indoor spaces.

69. On January 5, 2022 Bush received an email message from Boch Center announcing a new COVID-19 Policy and Safety Measures including that starting January 15th, 2022, "per the City of Boston's new vaccine requirement for indoor spaces… For patrons ages 12 and up, full vaccination is required to attend any performance." (See Exhibit 14.)

70. The Boch Center's January 5, 2022 email message did not include any accommodations for patrons' individual medical or religious needs or exemptions.

71. Bush submits that Mayor Wu and other municipal officials do not have the constitutional and/or legal authority to require people to show proof of vaccination to enter public spaces such as theaters.

72. No order, mandate, policy, or the like from government officials or private entities can supersede or override laws.

COUNT I

(Breach of Contract)

73. Bush incorporates by reference paragraphs one through 72 above as if fully restated herein.

74. In and around July of 2021, Boch Center offered tickets to upcoming shows at its theaters to Bush for a price.

75. When Bush accepted Boch Center's offer and tendered consideration by purchasing those tickets in July 2021, Boch Center communicated no conditions contingency (i.e. requirement) for Bush or other show guests to take medical tests, show proof of "vaccination" or wear face masks/coverings.

76. After Bush's ticket purchases, Boch Center communicated new conditions contingencies (i.e. requirements) of show guests to show proof of "COVID-19 vaccination" or a negative COVID test and wear face masks without prior warning to Bush.

77. By its conduct, Boch Center breached a valid contract with Bush.

78. Boch Center's conduct constitutes a material breach of the contract.

79. Bush has suffered and been damaged as a consequence of Boch Center's material breach complained of herein.

80. Bush is entitled to be made whole for and on account thereof.

WHEREFORE, the Plaintiff, Michael Bush, prays for judgment against the Defendant, The Wang Center for the Performing Arts, Inc., in an amount to be determined at trial and that he be awarded interest, costs and such other relief as this Court may deem just and proper.

COUNT II

(Violation of M.G.L. Ch. 272 §92A and §98)

81. Bush hereby incorporates by reference paragraphs one through 80 above, as if fully restated herein.

82. Boch Center's policy deprived certain customers including Bush of the "full enjoyment of the accommodations, advantages, facilities or privileges offered to the general public" in violation of civil right M.G.L. Ch. 272 §98.

83. Upon Bush having informed Boch Center its policy violated M.G.L. Ch. 272 §92A's and §98's prohibition against certain forms of discrimination, Boch Center failed to take any action to bring its policy into conformance with those laws.

84. As a direct and proximate result of Boch Center's policy's violation of Bush's civil rights under those laws, Bush has been damaged.

WHEREFORE, the Plaintiff, Michael Bush, prays for:

1. Declaration that the Defendant's policy is unlawful and void,
2. This Court to enjoin the Defendant from religious and medical discrimination, and
3. Judgement against the Defendant, The Wang Center for the Performing Arts, Inc., in an amount to be determined at trial and that Bush be awarded interest, costs and such other relief as this Court may deem just and proper.

COUNT III

(Breach of Covenant of Good Faith and Fair Dealing)

85. Bush hereby incorporates by reference paragraphs one through 84 above, as if fully restated herein.

86. By its conduct, Boch Center breached the covenant of good faith and fair dealing.

87. As a direct and proximate result of Boch Center's failure to exercise good faith and fair dealing, Mr. Bush has been damaged.

WHEREFORE, the Plaintiff, Michael Bush, prays for judgment against the Defendant, The Wang Center for the Performing Arts, Inc., in an amount to be determined at trial and that he be awarded interest, costs and such other relief as this Court may deem just and proper.

COUNT IV

(Violation of Title 18 U.S.C. § 242 and 42 U.S.C. § 1983)

88. Bush hereby incorporates by reference paragraphs one through 87 above, as if fully restated herein.

89. Boch Center had reason to know its policy violated Bush's legal rights under Title III of the Americans with Disabilities Act and M.G.L. Ch. 272 §92A, as Bush's M.G.L. Ch. 93A Notice and Demand letter informed Boch Center of that.

90. After receiving Bush's M.G.L. Ch. 93A Notice and Demand Letter, Boch Center failed to act to bring its policy into conformance with applicable laws or to rectify its violation of Bush's legal rights.

91. Boch Center used Boston Public Health Commission's Order Requiring Face Coverings In The City Of Boston dated August 20, 2021 as justification for its face mask policy.

92. That Boston Public Health Commission Order stated that, "face coverings are not required for children under two years of age, anyone who has trouble breathing, anyone who is unconscious, incapacitated or otherwise unable to remove the mask without assistance, or anyone who due to disability is unable to wear a mask."

93. Boch Center's policy allowed for none of the exemptions the Boston Public Health Commission Order specified.

94. Boch Center used Boston Mayor Wu's announced proof of COVID-19 vaccination for entry to certain public indoor spaces procedure as justification for the Boch Center's new policy announced in its January 5th, 2022 email message to Bush.

95. Boch Center used the color of law (specifically, the Boston Public Health Commission Order and Boston Mayor Wu's announced COVID-19 proof of COVID-19 vaccination for entry procedure) to violate Bush's legal rights.

96. Demonstrating utter contempt for Bush's legal rights he had communicated in his M.G.L. Ch. 93A Notice and Demand letter, Boch Center unilaterally took Bush's tickets away and issued him a refund for his Cirque Dreams Holidaze show tickets' purchase price—despite Bush having communicated he wanted his legal rights honored, not a refund.

97. Bush has been severely damaged as a result of Boch Center's violations of his legal rights under the color of law.

98. Ordinary damages and reimbursement of legal expenses would be insufficient to compensate Bush for Boch Center's violations of Bush's civil rights and insufficient to deter Boch Center from further such civil rights violations.

WHEREFORE, the Plaintiff, Michael Bush, demands judgment enter against the Defendant, The Wang Center for the Performing Arts, Inc., for compensatory, presumed, and/or punitive damages pursuant to 42 U.S.C. §1983 in the amount of $800,000 in addition to any other damages or relief awarded.

COUNT V

(Misrepresentation)

99. Bush hereby incorporates by reference paragraphs one through 98 above, as if fully restated herein.

100. Boch Center made materially false representations to Bush to induce him to enter into a consumer transaction with Boch Center.

101. Boch Center made the false representations with the intention that Bush would rely on the same, to his detriment, in making his decision to engage in the transaction and make payment on the same.

102. In making his decision, Bush did in fact rely on Boch Center's representations as true, and such reliance was reasonable under the circumstances.

103. As a result of Boch Center's intentional misrepresentations, Bush has been damaged.

WHEREFORE, the Plaintiff, Michael Bush demands judgment enter against the Defendant in an amount to be determined at trial, and that Plaintiff be awarded interest, costs, and such other relief as this Court may deem appropriate.

COUNT VI

(Violation of M.G.L. Chapter 93A)

104. Bush hereby incorporates by reference paragraphs one through 103 above, as if fully restated herein.

105. Boch Center is engaged in trade and commerce for the purposes of M.G.L. c. 93A.

106. Boch Center's conduct throughout this matter has been unfair and deceptive which conduct includes, but is not limited to, that which is set forth in the 93A Notice letter and the facts section set forth above and incorporated herein.

107. As a result of Boch Center's unfair and deceptive acts, Bush has been severely damaged in mind and body.

108. Boch Center's unfair and deceptive acts were committed in an intentional, willful and knowing manner.

109. There is no legitimate good faith defense that could tend to support or justify Boch Center's unfair and/or deceptive conduct.

WHEREFORE, the Plaintiff, Michael Bush, demands judgment enter against the Defendant in an amount to be determined at trial, and that he be awarded treble damages, interest, costs, attorney fees, and such other relief as this Court may deem just and proper.

Jury Claim

The Plaintiff, Michael Bush, requests that he be granted a trial by jury on all issues so triable.

Verification

I, Michael Bush, do hereby depose and swear that I have knowledge of each of the foregoing allegations and believe each of them to be true and accurate.

Michael Bush

Respectfully submitted,
Michael Bush,
By his Attorney,

Richard C. Chambers, Jr., Esq.
BBO#: 651251
Chambers Law Office
220 Broadway, Suite 404
Lynnfield, MA 01940
Office: (781) 581-2031
Cell: (781) 363-1773
Fax: (781) 581-8449
Richard@chamberslawoffice.com

Date: 1/28/22

Exhibit 1

U.S. FOOD & DRUG ADMINISTRATION

Our STN: BL 125742/0

BLA APPROVAL

August 23, 2021

BioNTech Manufacturing GmbH
Attention: Amit Patel
Pfizer Inc.
235 East 42nd Street
New York, NY 10017

Dear Mr. Patel:

Please refer to your Biologics License Application (BLA) submitted and received on May 18, 2021, under section 351(a) of the Public Health Service Act (PHS Act) for COVID-19 Vaccine, mRNA.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2229 to BioNTech Manufacturing GmbH, Mainz, Germany, under the provisions of section 351(a) of the PHS Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product, COVID-19 Vaccine, mRNA, which is indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT04368728 and NCT04380701.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture COVID-19 Vaccine, mRNA drug substance at Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC, 1 Burtt Road, Andover, Massachusetts. The final formulated product will be manufactured, filled, labeled and packaged at Pfizer Manufacturing Belgium NV, Rijksweg 12, Puurs, Belgium and at Pharmacia & Upjohn Company LLC, 7000 Portage Road, Kalamazoo, Michigan. The diluent, 0.9% Sodium Chloride Injection, USP, will be manufactured at Hospira, Inc., (b) (4) and at Fresenius Kabi USA, LLC, (b) (4).

You may label your product with the proprietary name, COMIRNATY, and market it in 2.0 mL glass vials, in packages of 25 and 195 vials.
We did not refer your application to the Vaccines and Related Biological Products Advisory Committee because our review of information submitted in your BLA, including the clinical study design and trial results, did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

DATING PERIOD

The dating period for COVID-19 Vaccine, mRNA shall be 9 months from the date of manufacture when stored between -90°C to -60°C (-130°F to -76°F). The date of manufacture shall be no later than the date of final sterile filtration of the formulated drug product (at Pharmacia & Upjohn Company LLC in Kalamazoo, Michigan, the date of manufacture is defined as the date of sterile filtration for the final drug product; at Pfizer Manufacturing Belgium NV in Puurs, Belgium, it is defined as the date of the (b) (4) Following the final sterile filtration, (b) (4) , no reprocessing/reworking is allowed without prior approval from the Agency. The dating period for your drug substance shall be (b) (4) when stored at (b) (4) We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

Please submit final container samples of the product in final containers together with protocols showing results of all applicable tests. You may not distribute any lots of product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to the Director, Office of Compliance and Biologics Quality, electronically through the eBPDR web application or at the address below. Links for the instructions on completing the electronic form (eBPDR) may be found on CBER's web site at https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/biological-product-deviations:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center

10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

MANUFACTURING CHANGES

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of COVID-19 Vaccine, mRNA, or in the manufacturing facilities.

LABELING

We hereby approve the draft content of labeling including Package Insert, submitted under amendment 74, dated August 21, 2021, and the draft carton and container labels submitted under amendment 63, dated August 19, 2021.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the final content of labeling (21 CFR 601.14) in Structured Product Labeling (SPL) format via the FDA automated drug registration and listing system, (eLIST) as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the Package Insert submitted on August 21, 2021. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELS

Please electronically submit final printed carton and container labels identical to the carton and container labels submitted on August 19, 2021, according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-certain-human-pharmaceutical-product-applications.

All final labeling should be submitted as Product Correspondence to this BLA STN BL 125742 at the time of use and include implementation information on Form FDA 356h.

ADVERTISING AND PROMOTIONAL LABELING

You may submit two draft copies of the proposed introductory advertising and promotional labeling with Form FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertising and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80), and you must submit distribution reports at monthly intervals as described in 21 CFR 600.81. For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format —Postmarketing Safety Reports for Vaccines* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-submissions-electronic-format-postmarketing-safety-reports-vaccines. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm061966.htm.

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric studies for ages younger than 16 years for this application because this product is ready for approval for use in individuals 16 years of age and older, and the pediatric studies for younger ages have not been completed.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported according to 21 CFR 601.28 and section 505B(a)(4)(C) of the FDCA. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

Label your annual report as an "**Annual Status Report of Postmarketing Study Requirement/Commitments**" and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements under section 506B of the FDCA are released or fulfilled. These required studies are listed below:

1. Deferred pediatric Study C4591001 to evaluate the safety and effectiveness of COMIRNATY in children 12 years through 15 years of age.

   Final Protocol Submission: October 7, 2020

   Study Completion: May 31, 2023

   Final Report Submission: October 31, 2023

2. Deferred pediatric Study C4591007 to evaluate the safety and effectiveness of COMIRNATY in infants and children 6 months to <12 years of age.

   Final Protocol Submission: February 8, 2021

   Study Completion: November 30, 2023

   Final Report Submission: May 31, 2024

3. Deferred pediatric Study C4591023 to evaluate the safety and effectiveness of COMIRNATY in infants <6 months of age.

   Final Protocol Submission: January 31, 2022

   Study Completion: July 31, 2024

   Final Report Submission: October 31, 2024

Submit the protocols to your IND 19736, with a cross-reference letter to this BLA STN BL 125742 explaining that these protocols were submitted to the IND. Please refer to the PMR sequential number for each study/clinical trial and the submission number as shown in this letter.
Submit final study reports to this BLA STN BL 125742. In order for your PREA PMRs to be considered fulfilled, you must submit and receive approval of an efficacy or a labeling

supplement. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated as:

- **Required Pediatric Assessment(s)**

We note that you have fulfilled the pediatric study requirement for ages 16 through 17 years for this application.

POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the FDCA will not be sufficient to assess known serious risks of myocarditis and pericarditis and identify an unexpected serious risk of subclinical myocarditis.

Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, we have determined that you are required to conduct the following studies:

4. Study C4591009, entitled "A Non-Interventional Post-Approval Safety Study of the Pfizer-BioNTech COVID-19 mRNA Vaccine in the United States," to evaluate the occurrence of myocarditis and pericarditis following administration of COMIRNATY.

   We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this study according to the following schedule:

   Final Protocol Submission: August 31, 2021

   Monitoring Report Submission: October 31, 2022

   Interim Report Submission: October 31, 2023

   Study Completion: June 30, 2025

   Final Report Submission: October 31, 2025

5. Study C4591021, entitled "Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus

Disease 2019 (COVID-19) Vaccine," to evaluate the occurrence of myocarditis and pericarditis following administration of COMIRNATY.

We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: August 11, 2021

Progress Report Submission: September 30, 2021

Interim Report 1 Submission: March 31, 2022

Interim Report 2 Submission: September 30, 2022

Interim Report 3 Submission: March 31, 2023

Interim Report 4 Submission: September 30, 2023

Interim Report 5 Submission: March 31, 2024

Study Completion: March 31, 2024

Final Report Submission: September 30, 2024

6. Study C4591021 substudy to describe the natural history of myocarditis and pericarditis following administration of COMIRNATY.

   We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this study according to the following schedule:

   Final Protocol Submission: January 31, 2022

   Study Completion: March 31, 2024

   Final Report Submission: September 30, 2024

7. Study C4591036, a prospective cohort study with at least 5 years of follow-up for potential long-term sequelae of myocarditis after vaccination (in collaboration with Pediatric Heart Network).

   We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this study according to the following schedule:

   Final Protocol Submission: November 30, 2021

   Study Completion: December 31, 2026

Final Report Submission: May 31, 2027

8. Study C4591007 substudy to prospectively assess the incidence of subclinical myocarditis following administration of the second dose of COMIRNATY in a subset of participants 5 through 15 years of age.

   We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this assessment according to the following schedule:

   Final Protocol Submission: September 30, 2021

   Study Completion: November 30, 2023

   Final Report Submission: May 31, 2024

9. Study C4591031 substudy to prospectively assess the incidence of subclinical myocarditis following administration of a third dose of COMIRNATY in a subset of participants 16 to 30 years of age.

   We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this study according to the following schedule:

   Final Protocol Submission: November 30, 2021

   Study Completion: June 30, 2022

   Final Report Submission: December 31, 2022

Please submit the protocols to your IND 19736, with a cross-reference letter to this BLA STN BL 125742 explaining that these protocols were submitted to the IND. Please refer to the PMR sequential number for each study/clinical trial and the submission number as shown in this letter.

Please submit final study reports to the BLA. If the information in the final study report supports a change in the label, the final study report must be submitted as a supplement to this BLA STN BL 125742. For administrative purposes, all submissions related to these postmarketing studies required under section 505(o) must be submitted to this BLA and be clearly designated as:

- **Required Postmarketing Correspondence under Section 505(o)**
- **Required Postmarketing Final Report under Section 505(o)**
- **Supplement contains Required Postmarketing Final Report under Section 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise

undertaken to investigate a safety issue. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

You must describe the status in an annual report on postmarketing studies for this product. Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing requirement;
- the original milestone schedule for the requirement;
- the revised milestone schedule for the requirement, if appropriate;
- the current status of the requirement (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status for the study or clinical trial. The explanation should include how the study is progressing in reference to the original projected schedule, including, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

We will consider the submission of your annual report under section 506B of the FDCA and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in section 505(o) and 21 CFR 601.70. We remind you that to comply with section 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to periodically report on the status of studies or clinical trials required under section 505(o) may be a violation of FDCA section 505(o)(3)(E)(ii) and could result in regulatory action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We acknowledge your written commitments as described in your letter of August 21, 2021 as outlined below:

10. Study C4591022, entitled "Pfizer-BioNTech COVID-19 Vaccine Exposure during Pregnancy: A Non-Interventional Post-Approval Safety Study of Pregnancy and Infant Outcomes in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry."

    Final Protocol Submission: July 1, 2021

Study Completion: June 30, 2025

Final Report Submission: December 31, 2025

11. Study C4591007 substudy to evaluate the immunogenicity and safety of lower dose levels of COMIRNATY in individuals 12 through <30 years of age.

    Final Protocol Submission: September 30, 2021

    Study Completion: November 30, 2023

    Final Report Submission: May 31, 2024

12. Study C4591012, entitled "Post-emergency Use Authorization Active Safety Surveillance Study Among Individuals in the Veteran's Affairs Health System Receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine."

    Final Protocol Submission: January 29, 2021

    Study Completion: June 30, 2023

    Final Report Submission: December 31, 2023

13. Study C4591014, entitled "Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California."

    Final Protocol Submission: March 22, 2021

    Study Completion: December 31, 2022

    Final Report Submission: June 30, 2023

Please submit clinical protocols to your IND 19736, and a cross-reference letter to this BLA STN BL 125742 explaining that these protocols were submitted to the IND. Please refer to the PMC sequential number for each study/clinical trial and the submission number as shown in this letter.

If the information in the final study report supports a change in the label, the final study report must be submitted as a supplement. Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Commitment – Correspondence Study Update**
- **Postmarketing Commitment – Final Study Report**
- **Supplement contains Postmarketing Commitment – Final Study Report**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing commitment;
- the original schedule for the commitment;
- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please contact the Regulatory Project Manager for this application.

Sincerely,

Mary A. Malarkey
Director
Office of Compliance
and Biologics Quality
Center for Biologics
Evaluation and Research

Marion F. Gruber, PhD
Director
Office of Vaccines
Research and Review
Center for Biologics
Evaluation and Research

Exhibit D

Subject: Vaccine Requirements & Safety Updates

From: Boch Center - To: bmoc54@verizon.net - Cc: - Date: August 23, 2021 at 1:53 PM

Boch Center to Require All Guests to Be Vaccinated or Provide a Negative COVID Test

The Boch Center is committed to helping stop the spread of COVID-19 and announced it will require all patrons to be fully vaccinated or provide a negative COVID test taken within 72 hours of the show. Guests will be asked to show their vaccination card or test results and a government issued ID prior to entering an event at the Wang or Shubert Theatres. The new policy goes into effect on September 14. The Boch Center will also require all administrative staff members, ushers, security personnel, stagehands and vendors be fully vaccinated Masks will be required for all guests, regardless of vaccination status, per City of Boston guidelines.

Please note that restrictions and safety protocols may vary by performance. Be sure to visit your specific show's event details page and to carefully read our pre-performance emails for important information pertaining to your performance.

MORE INFO ON SAFETY

Boch Center is a 501(c)(3) nonprofit institution.

We are an innovator and guardian of iconic venues, providing relevant and inclusive performing arts entertainment and cultural educational experiences for the most diverse audiences possible.
Find A Show | Donate Today | Learn About Our Outreach Programs

Boch Center | 270 Tremont Street, Boston, MA 02116

Exhibit 3

To: Whom It May Concern
Re: Mask mandate
Date: September 14, 2021

I have interviewed and examined Mr. Michael Bush. I have found him to have contraindications to mask wearing for a private medical condition. He is therefore exempt from the mask mandate according to the letter from Governor Baker dated May 28, 2021.

Sincerely

John Diggs MD LLC
2030 Boston Road, Suite 2
Wilbraham MA 0195

Tel: 413-300-2233
Fax: 413-271-1132
Email: JohnDiggs@JohnDiggsMD.com

Exhibit 4

ORDER REQUIRING FACE COVERINGS IN THE CITY OF BOSTON

DATE OF ORDER: August 20, 2021

The Boston Public Health Commission, acting through its duly appointed and authorized agent, Interim Executive Director Rita Nieves, pursuant to M.G.L. c. 111, § 30, the Boston Public Health Act of 1995, M.G.L. c. 111 App §§ 2-6, M.G.L. c. 111 §§ 6, 7, 31, 95, 104, 122, 310 CMR 11.05, 105 CMR 300.200 and all other authorizing statutes as well as the Boston Public Health Commission's Declaration of a Public Health Emergency Relative to COVID-19 in the City of Boston dated March 15, 2020, as extended, hereby enacts and declares as follows:

Whereas, a Public Health Emergency due to the outbreak of the 2019 novel Coronavirus ("COVID-19") in the City of Boston pursuant to declaration of the Boston Public Health Commission dated March 15, 2020 and extended on April 24, 2020 remains in full force and effect;

Whereas, despite significant improvement in vaccination rates and other key health metrics since the height of the pandemic, there is clear evidence that COVID-19 continues to cause serious harm to the public health of the City of Boston;

Whereas, evidence indicates that the Delta variant is more transmissible than prior variants of the virus, may cause more severe illness, and that even fully vaccinated individuals can spread the virus to others;

Whereas, although evidence shows that even against the Delta variant, fully vaccinated individuals have substantial protection against severe illness, hospitalization, and death, in order to maximize protection from the Delta variant, the U.S. Centers for Disease Control and Prevention (CDC) recommends that all persons—regardless of vaccination status—wear face coverings indoors in areas of substantial or high transmission, as defined by the CDC;

Whereas, according to the CDC COVID Data Tracker, the level of community transmission in Suffolk County for the time period between August 9, 2021 and August 15, 2021 is categorized as high;

Whereas, the relevant agencies of the City of Boston, including the Boston Public Health Commission, have determined that further temporary measures are necessary to prevent the spread and resurgence of COVID-19 in Boston; and

Whereas, the intent of this Order is to prevent the spread of COVID-19 to the maximum extent possible. All provisions of this Order should be interpreted to effectuate this intent. Failure to comply with any of the provisions of this Order constitutes an imminent and immediate threat to public health.

THEREFORE, THE FOLLOWING PUBLIC HEALTH ORDER SHALL BE IN EFFECT FOR THE CITY OF BOSTON, AS FOLLOWS:

1. All persons shall wear a mask or face covering that covers their nose and mouth, such as a fabric or surgical mask, whenever they are indoors on the premises of a business, club, place of assembly or other place that is open to members of the public, including but not limited to retail establishments, restaurants, bars, performance venues, social clubs, event spaces, and municipal buildings.

2. Restaurant, indoor bar, and dance venue customers may only remove face coverings when they are actively eating or drinking. Patrons standing or ordering at the bar must be masked. Guests must be masked on indoor dance floors.

3. This Order shall not apply to informal gatherings at private residences in which no compensation for use of the property is paid to the owner.

4. Notwithstanding any provision in this Order, pursuant to guidance issued by the CDC, face coverings are not required for children under two years of age, anyone who has trouble breathing, anyone who is unconscious, incapacitated or otherwise unable to remove the mask without assistance, or anyone who due to disability is unable to wear a mask.

5. The mask requirement shall not apply to performers, while performing, provided that they are at least six feet away from any customers.

6. Additional guidance may be issued by the Boston Public Health Commission or any other designee agency to clarify and implement this Order.

7. This Order shall take effect on 8:00 a.m. on August 27th, 2021 and remain in effect until rescinded by the Executive Director, in their discretion.

ENFORCEMENT

All reasonable efforts will be made to secure voluntary compliance with this Order, however this Order may be enforced through an order of a court of competent jurisdiction. The Executive

Director may seek the assistance of other City of Boston agencies in ensuring compliance with this order.

NOTICE

The City of Boston must promptly provide copies of this Order by posting on the Boston Public Health Commission website (bphc.org) and providing a copy to any member of the public requesting one.

IT IS SO ORDERED: **Dated: August 20, 2021**

Rita Nieves
INTERIM EXECUTIVE DIRECTOR
BOSTON PUBLIC HEALTH COMMISSION

Exhibit 5

U.S. FOOD & DRUG ADMINISTRATION

December 16, 2021

Pfizer Inc.
Attention: Mr. Amit Patel
235 East 42nd St
New York, NY 10017

Dear Mr. Patel:

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act or the Act), the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes Coronavirus Disease 2019 (COVID-19).[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[2]

On December 11, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19 for individuals 16 years of age and older pursuant to Section 564 of the Act. FDA reissued the letter of authorization on: December 23, 2020,[3] February 25, 2021,[4] May

[1] U.S. Department of Health and Human Services, Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the FD&C Act, 21 U.S.C. § 360bbb-3, February 4, 2020.

[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).

[3] In the December 23, 2020 revision, FDA removed reference to the number of doses per vial after dilution from the letter of authorization, clarified the instructions for vaccination providers reporting to VAERS, and made other technical corrections. FDA also revised the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) to clarify the number of doses of vaccine per vial after dilution and the instructions for reporting to VAERS. In addition, the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) and the Fact Sheet for Recipients and Caregivers were revised to include additional information on safety monitoring and to clarify information about the availability of other COVID-19 vaccines.

[4] In the February 25, 2021 revision, FDA allowed flexibility on the date of submission of monthly periodic safety reports and revised the requirements for reporting of vaccine administration errors by Pfizer Inc. The Fact Sheet for Health Care Providers Administering Vaccine (Vaccination Providers) was revised to provide an update to the storage and transportation temperature for frozen vials, direct the provider to the correct CDC website for information on monitoring vaccine recipients for the occurrence of immediate adverse reactions, to include data from a developmental toxicity study, and add adverse reactions that have been identified during post authorization use. The Fact Sheet for Recipients and Caregivers was revised to add adverse reactions that have been identified during post authorization use.

10, 2021,[5] June 25, 2021,[6] and August 12, 2021.[7] On August 23, 2021, FDA approved COMIRNATY (COVID-19 Vaccine, mRNA)[8] and reissued the letter in its entirety for both Pfizer-BioNTech COVID-19 Vaccine and certain uses of COMIRNATY (COVID-19 Vaccine, mRNA).[9] Subsequently, FDA reissued the letter of authorization on September 22, 2021,[10]

---

[5] In the May 10, 2021 revision, FDA authorized Pfizer-BioNTech Vaccine for the prevention of COVID-19 in individuals 12 through 15 years of age, as well as for individuals 16 years of age and older. In addition, FDA revised the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) to include the following Warning: "Syncope (fainting) may occur in association with administration of injectable vaccines, in particular in adolescents. Procedures should be in place to avoid injury from fainting." In addition, the Fact Sheet for Recipients and Caregivers was revised to instruct vaccine recipients or their caregivers to tell the vaccination provider about fainting in association with a previous injection.

[6] In the June 25, 2021 revision, FDA clarified terms and conditions that relate to export of Pfizer-BioNTech COVID-19 Vaccine from the United States. In addition, the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) was revised to include a Warning about myocarditis and pericarditis following administration of the Pfizer-BioNTech COVID-19 Vaccine. The Fact Sheet for Recipients and Caregivers was updated to include information about myocarditis and pericarditis following administration of the Pfizer-BioNTech COVID-19 Vaccine.

[7] In the August 12, 2021 revision, FDA authorized a third dose of the Pfizer-BioNTech COVID-19 Vaccine administered at least 28 days following the two dose regimen of this vaccine in individuals 12 years of age or older who have undergone solid organ transplantation, or individuals 12 years of age or older who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

[8] COMIRNATY (COVID-19 Vaccine, mRNA) was approved for active immunization to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older.

[9] In the August 23, 2021 revision, FDA clarified that, subsequent to the FDA approval of COMIRNATY (COVID-19 Vaccine, mRNA) for the prevention of COVID-19 for individuals 16 years of age and older, this EUA would remain in place for the Pfizer-BioNTech COVID-19 Vaccine for the previously-authorized indication and uses. It also authorized COMIRNATY (COVID-19 Vaccine, mRNA) under this EUA for certain uses that are not included in the approved biologics license application (BLA). In addition, the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) was revised to provide updates on expiration dating of the authorized Pfizer-BioNTech COVID-19 Vaccine and updated language regarding warnings and precautions related to myocarditis and pericarditis. The Fact Sheet for Recipients and Caregivers was updated as the Vaccine Information Fact Sheet for Recipients and Caregivers, which comprises the Fact Sheet for the authorized Pfizer-BioNTech COVID-19 Vaccine and information about the FDA-licensed vaccine, COMIRNATY (COVID-19 Vaccine, mRNA).

[10] In the September 22, 2021 revision, FDA authorized the administration of a single booster dose of COMIRNATY (COVID-19 Vaccine, mRNA) or Pfizer-BioNTech COVID-19 Vaccine at least 6 months after completing the primary series of this vaccine in individuals: 65 years of age and older; 18 through 64 years of age at high risk of severe COVID-19; and 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19.

October 20, 2021,[11] October 29, 2021,[12] November 19, 2021,[13] and December 9, 2021.[14]

On December 16, 2021, FDA approved a supplement to the COMIRNATY (COVID-19 Vaccine, mRNA) BLA to include a new 30 microgram dose formulation of COMIRNATY (COVID-19 Vaccine, mRNA) that uses Tris buffer in addition to the PBS buffer used in the originally approved vaccine.

On December 16, 2021, having concluded that revising this EUA is appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA is again reissuing the December 13, 2021 letter of authorization in its entirety with revisions incorporated to amend the EUA for COMIRNATY (COVID-19 Vaccine, mRNA) and Pfizer-BioNTech COVID-19 Vaccine to clarify that the Pfizer-BioNTech COVID-19 Vaccine that uses Tris buffer and COMIRNATY (COVID-19 Vaccine, mRNA) that uses the Tris buffer have the same formulation and can be used interchangeably. In addition, FDA is: extending the expiration date of the Pfizer-BioNTech COVID-19 Vaccine that uses the Tris buffer from 6 months to 9 months when held at -90 °C to -60 °C; revising the Fact Sheets for Healthcare Providers Administering Vaccine (Vaccination Providers) to include information on the updated expiration dating of the formulation of the Pfizer-BioNTech COVID-19 Vaccine that uses the Tris buffer; and updating the Fact Sheet for Recipients and Caregivers to provide information on the formulation of COMIRNATY (COVID-19 Vaccine, mRNA) that uses the Tris buffer. The authorized uses, as well as the two formulations that have three presentations, are described in the Scope of Authorization section of this letter (Section II).

---

[11] In the October 20, 2021 revision, FDA clarified eligibility for the booster dose of COMIRNATY (COVID-19 Vaccine, mRNA) or Pfizer-BioNTech COVID-19 Vaccine and authorized the administration of a single booster dose of Pfizer-BioNTech COVID-19 Vaccine or COMIRNATY (COVID-19 Vaccine, mRNA) as a heterologous booster dose following completion of primary vaccination with another authorized COVID-19 vaccine. The eligible population(s) and dosing interval for the heterologous booster dose are the same as those authorized for a booster dose of the vaccine used for primary vaccination.

[12] In the October 29, 2021 revision, FDA authorized: 1) the use of Pfizer-BioNTech COVID-19 Vaccine for children 5 through 11 years of age; and 2) a manufacturing change to include an additional formulation of the Pfizer-BioNTech COVID-19 Vaccine that uses tromethamine (Tris) buffer instead of phosphate buffered saline (PBS) used in the originally authorized Pfizer-BioNTech COVID-19 Vaccine. The formulation of the Pfizer-BioNTech COVID-19 Vaccine that uses Tris buffer was authorized in two presentations: 1) Multiple dose vials, with gray caps and labels with a gray border, formulated to provide, without need for dilution, doses (each 0.3 mL dose containing 30 mg nucleoside-modified messenger RNA (modRNA)) for individuals 12 years of age and older; and 2) Multiple dose vials, with orange caps and labels with an orange border, formulated to provide, after dilution, doses (each 0.2 mL dose containing 10 µg modRNA) for individuals 5 through 11 years of age. The formulation that uses Tris buffer is the only formulation that is authorized for use in individuals 5 through 11 years of age.

[13] In the November 19, 2021 revision, FDA authorized the use of COMIRNATY (COVID-19 Vaccine, mRNA) and the Pfizer-BioNTech COVID-19 Vaccine as a single booster dose in individuals 18 years of age or older at least 6 months after completing the primary series of this vaccine (i.e., as a homologous booster dose), and as a single booster dose following completion of primary vaccination with another authorized COVID-19 vaccine (i.e., as a heterologous booster dose) in individuals 18 years of age or older. The dosing interval for the heterologous booster dose is the same as that authorized for a booster dose of the vaccine used for primary vaccination.

[14] In the December 9, 2021 revision, FDA authorized the use of the vaccine as a single booster dose in individuals 16 and 17 years of age, at least 6 months after completing the primary series of this vaccine (i.e., as a homologous booster dose).

For the December 11, 2020 authorization for individuals 16 years of age and older, FDA reviewed safety and effectiveness data from an ongoing Phase 1/2/3 trial in approximately 44,000 participants randomized 1:1 to receive Pfizer-BioNTech COVID-19 Vaccine or saline control. The trial enrolled participants 12 years of age and older. FDA's review at that time considered the safety and effectiveness data as they relate to the request for emergency use authorization in individuals 16 years of age and older. FDA's review of the available safety data from 37,586 of the participants 16 years of age and older, who were followed for a median of two months after receiving the second dose, did not identify specific safety concerns that would preclude issuance of an EUA. FDA's analysis of the available efficacy data from 36,523 participants 12 years of age and older without evidence of SARS-CoV-2 infection prior to 7 days after dose 2 confirmed that the vaccine was 95% effective (95% credible interval 90.3, 97.6) in preventing COVID-19 occurring at least 7 days after the second dose (with 8 COVID-19 cases in the vaccine group compared to 162 COVID-19 cases in the placebo group). Based on these data, and review of manufacturing information regarding product quality and consistency, FDA concluded that it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine may be effective. Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine outweigh the known and potential risks of the vaccine, for the prevention of COVID-19 in individuals 16 years of age and older. Finally, on December 10, 2020, the Vaccines and Related Biological Products Advisory Committee voted in agreement with this conclusion.

For the May 10, 2021 authorization for individuals 12 through 15 years of age, FDA reviewed safety and effectiveness data from the above-referenced, ongoing Phase 1/2/3 trial that enrolled approximately 46,000 participants, including 2,260 participants 12 through 15 years of age. Trial participants were randomized 1:1 to receive Pfizer-BioNTech COVID-19 Vaccine or saline control. FDA's review of the available safety data from 2,260 participants 12 through 15 years of age, who were followed for a median of 2 months after receiving the second dose, did not identify specific safety concerns that would preclude issuance of an EUA. FDA's analysis of SARS-CoV-2 50% neutralizing antibody titers 1 month after the second dose of Pfizer-BioNTech COVID-19 Vaccine in a subset of participants who had no serological or virological evidence of past SARS-CoV-2 infection confirm that the geometric mean antibody titer in participants 12 through 15 years of age was non-inferior to the geometric mean antibody titer in participants 16 through 25 years of age. FDA's analysis of available descriptive efficacy data from 1,983 participants 12 through 15 years of age without evidence of SARS-CoV-2 infection prior to 7 days after dose 2 confirm that the vaccine was 100% effective (95% confidence interval 75.3, 100.0) in preventing COVID-19 occurring at least 7 days after the second dose (with no COVID-19 cases in the vaccine group compared to 16 COVID-19 cases in the placebo group). Based on these data, FDA concluded that it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine may be effective in individuals 12 through 15 years of age. Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine outweigh the known and potential risks of the vaccine, for the prevention of COVID-19 in individuals 12 through 15 years of age.

For the August 12, 2021 authorization of a third primary series dose in individuals 12 years of age or older who have undergone solid organ transplantation, or individuals 12 years of age or older who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise, FDA reviewed safety and effectiveness data reported in two manuscripts on solid organ transplant recipients. The first study was a single arm study conducted in 101 individuals who had undergone various solid organ transplant procedures (heart, kidney, liver, lung, pancreas) a median of 97±8 months earlier. A third dose of the Pfizer-BioNTech COVID-19 Vaccine was administered to 99 of these individuals approximately 2 months after they had received a second dose. Levels of total SARS-CoV-2 binding antibodies meeting the pre-specified criteria for success occurred four weeks after the third dose in 26/59 (44.0%) of those who were initially considered to be seronegative and received a third dose of the Pfizer-BioNTech COVID-19 Vaccine; 67/99 (68%) of the entire group receiving a third vaccination were subsequently considered to have levels of antibodies indicative of a significant response. In those who received a third vaccine dose, the adverse event profile was similar to that after the second dose and no grade 3 or grade 4 events were reported. A supportive secondary study describes a double-blind, randomized-controlled study conducted in 120 individuals who had undergone various solid organ transplant procedures (heart, kidney, kidney-pancreas, liver, lung, pancreas) a median of 3.57 years earlier (range 1.99-6.75 years). A third dose of a similar messenger RNA vaccine (the Moderna COVID-19 vaccine) was administered to 60 individuals approximately 2 months after they had received a second dose (i.e., doses at 0, 1 and 3 months); saline placebo was given to 60 individuals for comparison. The primary outcome was anti-RBD antibody at 4 months greater than 100 U/mL. This titer was selected based on NHP challenge studies as well as a large clinical cohort study to indicate this antibody titer was protective. Secondary outcomes were based on a virus neutralization assay and polyfunctional T cell responses. Baseline characteristics were comparable between the two study arms as were pre-intervention anti-RBD titer and neutralizing antibodies. Levels of total SARS-CoV-2 binding antibodies indicative of a significant response occurred four weeks after the third dose in 33/60 (55.0%) of the Moderna COVID-19 vaccinated group and 10/57 (17.5%) of the placebo individuals. In the 60 individuals who received a third vaccine dose, the adverse event profile was similar to that after the second dose and no grade 3 or grade 4 adverse events were reported. Despite the moderate enhancement in antibody titers, the totality of data (i.e., supportive paper by Hall et al. demonstrated efficacy of the product in the elderly and persons with co-morbidities) supports the conclusion that a third dose of the Pfizer-BioNTech COVID-19 Vaccine may be effective in this population, and that the known and potential benefits of a third dose of Pfizer-BioNTech COVID-19 Vaccine outweigh the known and potential risks of the vaccine for immunocompromised individuals at least 12 years of age who have received two doses of the Pfizer-BioNTech COVID-19 Vaccine and who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

For the September 22, 2021 authorization of a single booster dose administered at least 6 months after completing the primary series in individuals: 65 years of age and older; 18 through 64 years of age at high risk of severe COVID-19; and 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19, FDA reviewed safety and effectiveness data from the above-referenced, ongoing Phase 1/2/3 trial in which 329 participants

18 through 75 years of age received a booster dose of the Pfizer-BioNTech COVID-19 Vaccine approximately 6 months (range 4.8 to 8.8 months) after completion of the primary series. FDA's review of the available safety data from 329 participants 18 through 75 years of age, who had been followed for a median of 2.6 months after receiving the booster dose, did not identify specific safety concerns that would preclude issuance of an EUA. The effectiveness of the booster dose of the Pfizer-BioNTech COVID-19 Vaccine is based on an assessment of 50% neutralizing antibody titers (NT50) against SARS-CoV-2 (USA_WA1/2020). FDA's analysis of SARS-CoV-2 NT50 one month after the booster dose compared to 1 month after the primary series in study participants 18 through 55 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster dose confirmed noninferiority for both geometric mean ratio and difference in seroresponse rates. Based on the totality of the scientific evidence available, including data from the above-referenced clinical trial, FDA concluded that a booster dose the Pfizer-BioNTech COVID-19 Vaccine may be effective, and that the known and potential benefits of a single booster dose at least 6 months after completing the primary series outweigh the known and potential risks for individuals 65 years of age and older; individuals 18 through 64 years of age at high risk of severe COVID-19; and individuals 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19.

For the October 20, 2021 authorization of a single booster dose as a heterologous booster dose following completion of primary vaccination with another authorized COVID-19 vaccine, FDA reviewed data from an ongoing Phase1/2 clinical trial in participants 19-85 years of age. In this trial, adults who had completed primary vaccination with a Moderna COVID-19 Vaccine 2-dose series (N=151), a Janssen COVID-19 Vaccine single dose (N=156), or a Pfizer-BioNTech COVID-19 Vaccine 2-dose series (N=151) at least 12 weeks prior to enrollment and who reported no history of SARS-CoV-2 infection were randomized 1:1:1 to receive a booster dose of one of three vaccines: Moderna COVID-19 Vaccine, Janssen COVID-19 Vaccine, or Pfizer-BioNTech COVID-19 Vaccine. Adverse events were assessed through 28 days after the booster dose. An overall review of adverse reactions reported following the Pfizer-BioNTech COVID-19 Vaccine heterologous booster dose did not identify any new safety concerns, as compared with adverse reactions reported following Pfizer-BioNTech COVID-19 Vaccine primary series doses or homologous booster dose. Neutralizing antibody titers, as measured by a pseudovirus neutralization assay using a lentivirus expressing the SARS-CoV-2 Spike protein with D614G mutation, were assessed on Day 1 prior to administration of the booster dose and on Day 15 after the booster dose. A booster response to the Pfizer-BioNTech COVID-19 Vaccine was demonstrated regardless of primary vaccination. Based on the on the totality of the scientific evidence available, including data from the above-referenced clinical trial, FDA concluded that a heterologous booster dose of the Pfizer-BioNTech COVID-19 Vaccine may be effective, and that the known and potential benefits of a heterologous booster dose of the Pfizer-BioNTech COVID-19 Vaccine following completion of primary vaccination with another authorized COVID-19 vaccine outweigh the known and potential risks.

For the October 29, 2021 authorization for the Pfizer-BioNTech COVID-19 Vaccine that uses Tris buffer for individuals 5 through 11 years of age, FDA reviewed safety and effectiveness data

from an ongoing Phase 1/2/3 trial that has enrolled 4,695 participants 5 through 11 years of age, of whom 3,109 participants received Pfizer-BioNTech COVID-19 Vaccine (containing 10 µg modRNA) formulated using PBS buffer and approximately 1,538 participants received saline control in Phase 2/3. FDA's review of the available safety data from 3,109 participants 5 through 11 years of age who received Pfizer-BioNTech COVID-19 Vaccine (containing 10 µg modRNA), including 1,444 who were followed for at least 2 months after receiving the second dose, did not identify specific safety concerns that would preclude issuance of an EUA. SARS-CoV-2 50% neutralizing antibody titers 1 month after the second dose were compared between a subset of participants 5 through 11 years of age who received Pfizer-BioNTech COVID-19 Vaccine (containing 10 µg modRNA) and a subset of participants 16 through 25 years of age who received Pfizer-BioNTech COVID-19 Vaccine (containing 30 µg modRNA) in the above-referenced ongoing Phase 1/2/3 trial that enrolled approximately 46,000 participants. Immunobridging analyses included a subset of participants from each study who had no serological or virological evidence of past SARS-CoV-2 infection. FDA's analyses confirm that immunobridging criteria were met for both geometric mean antibody titers and seroresponse rates. FDA's analysis of available descriptive efficacy data from 1,968 participants 5 through 11 years of age without evidence of SARS-CoV-2 infection prior to 7 days after dose 2 confirm that the vaccine was 90.7% effective (95% confidence interval 67.7, 98.3) in preventing COVID-19 occurring at least 7 days after the second dose (with 3 COVID-19 cases in the vaccine group compared to 16 COVID-19 cases in the placebo group). Based on these data, FDA concluded that it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine may be effective in individuals 5 through 11 years of age. Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine outweigh the known and potential risks of the vaccine, for the prevention of COVID-19 in individuals 5 through 11 years of age. Finally, on October 26, 2021, the Vaccines and Related Biological Products Advisory Committee voted in agreement with this conclusion.

For the October 29, 2021 authorization of the manufacturing change to include an additional formulation of the Pfizer-BioNTech COVID-19 Vaccine that uses Tris buffer instead of PBS buffer used in the originally authorized Pfizer-BioNTech COVID-19 Vaccine, FDA reviewed data on analytical comparability, which uses laboratory testing to demonstrate that a change in product formulation is not expected to impact safety or effectiveness. In the case of Pfizer-BioNTech COVID-19 Vaccine, multiple different release parameters were evaluated, ranging from product appearance to size of the lipid-nanoparticle to the integrity of the modRNA in the product. Release and characterization tests include tests for purity, composition, and critical attributes of mRNA associated with the activity of the vaccine. In this case, analytical comparability to the current PBS formulation of the Pfizer-BioNTech COVID-19 Vaccine was demonstrated for the Tris formulation of the Pfizer-BioNTech COVID-19 Vaccine through a combination of release and characterization testing.

For the November 19, 2021 authorization expanding the eligible population for the homologous and heterologous booster doses to individuals 18 years of age and older, FDA reviewed data provided by the sponsor and other data available to FDA, including real world evidence. Data previously reviewed to support the September 22, 2021 authorization of a homologous booster dose, together with new real-world data indicating increasing COVID-19 cases in the United

States, including among vaccinated individuals, and suggesting a decreased risk of myocarditis following mRNA COVID-19 vaccine booster doses compared with second primary series doses, support expansion of the population eligible for a Pfizer-BioNTech COVID-19 vaccine homologous booster dose to include all individuals 18 years of age and older who completed the primary series at least 6 months previously. Data previously reviewed to support the October 20, 2021 authorization of a heterologous booster dose, together with data and information to support authorization of the EUA amendment to expand the eligible population for a homologous booster dose of the Moderna COVID-19 Vaccine, support a revision to the Pfizer-BioNTech COVID-19 Vaccine EUA such that the eligible population for a heterologous booster dose of the Pfizer-BioNTech COVID-19 Vaccine is all adults 18 years of age and older who completed primary vaccination with another authorized COVID-19 vaccine. Based on the totality of the scientific evidence available, FDA concludes that a homologous or heterologous booster dose of the Pfizer-BioNTech COVID-19 Vaccine may be effective, and that the known and potential benefits of the booster dose of the Pfizer-BioNTech Vaccine following completion of primary vaccination with Pfizer-BioNTech COVID-19 Vaccine or another authorized COVID-19 vaccine, outweigh the known and potential risks in individuals 18 years of age and older.

For the December 9, 2021 authorization expanding the eligible population for the homologous booster doses to individuals 16 years of age and older, FDA reviewed: data submitted previously by the sponsor to support the September 22, 2021 and November 19, 2021 authorization of a homologous booster dose under EUA; real-world data, which includes data that indicates increasing COVID-19 cases in the United States amongst vaccinated and unvaccinated individuals, and data suggesting a decreased risk of myocarditis following administration of Pfizer-BioNTech COVID-19 Vaccine booster doses compared with second primary series doses among vaccinated individuals; and a benefit-risk assessment from the sponsor, to support the expansion of the population eligible for a Pfizer-BioNTech COVID-19 Vaccine homologous booster dose to include all individuals 16 years of age and older who completed the primary series at least 6 months previously. Based on the totality of the scientific evidence available, FDA concludes that a homologous booster dose of the Pfizer-BioNTech COVID-19 Vaccine may be effective, and that the known and potential benefits of the booster dose of the Pfizer-BioNTech COVID-19 Vaccine following completion of primary vaccination with Pfizer-BioNTech COVID-19 Vaccine outweigh the known and potential risks in individuals 16 years of age and older.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of Pfizer-BioNTech COVID-19 Vaccine[15] for the prevention of COVID-19, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization. Additionally, as specified in subsection III.BB., I am authorizing use of COMIRNATY (COVID-19 Vaccine, mRNA)[16] under this EUA as described in the Scope of Authorization section of this letter (Section II).

---

[15] Reference to the Pfizer-BioNTech COVID-19 Vaccine hereinafter refers to both the formulations that use the PBS and Tris buffers, unless specifically delineated otherwise.

[16] Reference to COMIRNATY (COVID-19 Vaccine, mRNA) hereinafter refers to both the formulations that use the PBS and Tris buffers, unless specifically delineated otherwise.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of Pfizer-BioNTech COVID-19 Vaccine[17] for the prevention of COVID-19 when administered as described in the Scope of Authorization (Section II) meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

A. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

B. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine may be effective in preventing COVID-19, and that, when used under the conditions described in this authorization, the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine when used to prevent COVID-19 outweigh its known and potential risks; and

C. There is no adequate, approved, and available alternative[18] Pfizer-BioNTech COVID-19 Vaccine to prevent COVID-19.[19]

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Pfizer Inc. will supply Pfizer-BioNTech COVID-19 Vaccine either directly or through authorized distributor(s),[20] to emergency response stakeholders[21] as directed by the U.S.

---

[17] In this section (Section I), references to Pfizer-BioNTech COVID-19 Vaccine also apply to COMIRNATY (COVID-19 Vaccine, mRNA).

[18] Although COMIRNATY (COVID-19 Vaccine, mRNA) is approved to prevent COVID-19 in individuals 16 years of age and older, there is not sufficient approved vaccine available for distribution to this population in its entirety at the time of reissuance of this EUA. Additionally, there are no COVID-19 vaccines that are approved to provide: COVID-19 vaccination in individuals 5 through 15 years of age; a third primary series dose to certain immunocompromised populations described in this EUA; a homologous booster dose to the authorized population described in this EUA; or a heterologous booster dose following completion of primary vaccination with another authorized COVID-19 vaccine.

[19] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.

[20] "Authorized Distributor(s)" are identified by Pfizer Inc. or, if applicable, by a U.S. government entity, such as the Centers for Disease Control and Prevention (CDC) and/or other designee, as an entity or entities allowed to distribute authorized Pfizer-BioNTech COVID-19 Vaccine.

[21] For purposes of this letter, "emergency response stakeholder" refers to a public health agency and its delegates that have legal responsibility and authority for responding to an incident, based on political or geographical boundary lines (e.g., city, county, tribal, territorial, State, or Federal), or functional (e.g., law enforcement or public health range) or sphere of authority to administer, deliver, or distribute vaccine in an emergency situation. In some cases (e.g., depending on a state or local jurisdiction's COVID-19 vaccination response organization and plans), there might be overlapping roles and responsibilities among "emergency response stakeholders" and "vaccination providers" (e.g., if a local health department is administering COVID-19 vaccines; if a pharmacy is acting in an official capacity under the authority of the state health department to administer COVID-19 vaccines). In such

government, including the Centers for Disease Control and Prevention (CDC) and/or other designee, for use consistent with the terms and conditions of this EUA; and

- Pfizer-BioNTech COVID-19 Vaccine may be administered by a vaccination provider[22] without an individual prescription for each vaccine recipient.

For use in individuals 12 years of age and older

- The Pfizer-BioNTech COVID-19 Vaccine formulations that use Tris and PBS buffers (each 0.3 mL dose containing 30 µg modRNA), as described in more detail under *Product Description* below, covered by this authorization will be administered by vaccination providers and used only to prevent COVID-19 in individuals 12 years of age and older with a two-dose primary regimen (3 weeks apart) and to provide:
    - a third primary series dose at least 28 days following the second dose to individuals 12 years of age or older who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise;
    - a single booster dose at least 6 months after completion of a primary series of the vaccine to individuals 16 years of age or older; and
    - a single booster dose as a heterologous booster dose following completion of primary vaccination with another authorized COVID-19 vaccine in individuals 18 years of age and older, where the dosing interval for the heterologous booster dose is the same as that authorized for a booster dose of the vaccine used for primary vaccination.

For use in individuals 5 through 11 years of age

- The Pfizer-BioNTech COVID-19 Vaccine that uses Tris buffer (each 0.2 mL dose containing 10 µg modRNA), as described in more detail under *Product Description* below, covered by this authorization will be administered by vaccination providers and used only to prevent COVID-19 in individuals 5 through 11 years of age with a two-dose primary regimen (3 weeks apart).

---

cases, it is expected that the conditions of authorization that apply to emergency response stakeholders and vaccination providers will all be met.

[22] For purposes of this letter, "vaccination provider" refers to the facility, organization, or healthcare provider licensed or otherwise authorized by the emergency response stakeholder (e.g., non-physician healthcare professionals, such as nurses and pharmacists pursuant to state law under a standing order issued by the state health officer) to administer or provide vaccination services in accordance with the applicable emergency response stakeholder's official COVID-19 vaccination and emergency response plan(s) and who is enrolled in the CDC COVID-19 Vaccination Program. If the vaccine is exported from the United States, a "vaccination provider" is a provider that is authorized to administer this vaccine in accordance with the laws of the country in which it is administered. For purposes of this letter, "healthcare provider" also refers to a person authorized by the U.S. Department of Health and Human Services (e.g., under the PREP Act Declaration for Medical Countermeasures against COVID-19) to administer FDA-authorized COVID-19 vaccine (e.g., qualified pharmacy technicians and State-authorized pharmacy interns acting under the supervision of a qualified pharmacist). See, e.g., HHS. *Fourth Amendment to the Declaration Under the Public Readiness and Emergency Preparedness Act for Medical Countermeasures Against COVID-19 and Republication of the Declaration*. 85 FR 79190 (December 9, 2020).

For use in individuals who are 11 years old at the time of the first dose, and turn 12 years old before the second dose:

- Notwithstanding the age limitations for use of the different formulations and presentations described above, individuals who will turn from 11 years to 12 years of age between their first and second dose in the primary regimen may receive, for either dose, either: (1) the Pfizer-BioNTech COVID-19 Vaccine that uses Tris buffer (each 0.2 mL dose containing 10 µg modRNA) covered by this authorization; or (2) the Pfizer-BioNTech COVID-19 Vaccine and COMIRNATY (COVID-19 Vaccine, mRNA) formulations provided in one of the presentations for individuals 12 years of age and older (each 0.3 mL dose containing 30 µg modRNA) covered by this authorization.
- The vaccine will be administered by vaccination providers and used only to prevent COVID-19 with a two-dose primary regimen (3 weeks apart).

This authorization also covers the use of the licensed COMIRNATY (COVID-19 Vaccine, mRNA) product when used to provide: (1) a two-dose primary regimen (0.3 mL each, 3 weeks apart) for individuals 12 through 15 years of age; (2) a third primary series dose at least 28 days following the second dose to individuals 12 years of age or older who have undergone solid organ transplantation or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise; (3) a single booster dose (0.3 mL) at least 6 months after completion of the primary series to individuals 16 years of age and older; and (4) a single booster dose (0.3 mL) as a heterologous booster dose following completion of primary vaccination with another authorized COVID-19 vaccine in individuals 18 years of age and older, where the dosing interval for the heterologous booster dose is the same as that authorized for a booster dose of the vaccine used for primary vaccination.

The Pfizer-BioNTech COVID-19 Vaccine that uses PBS buffer and COMIRNATY (COVID-19 Vaccine, mRNA) that uses PBS buffer have the same formulation. Additionally, the Pfizer-BioNTech COVID-19 Vaccine that uses Tris buffer and COMIRNATY (COVID-19 Vaccine, mRNA) that uses Tris buffer have the same formulation. The products are legally distinct with certain differences that do not impact safety or effectiveness. Accordingly, under this EUA, the Pfizer-BioNTech COVID-19 Vaccine that uses PBS buffer and COMIRNATY (COVID-19 Vaccine, mRNA) that uses PBS buffer can be used interchangeably, and the Pfizer-BioNTech COVID-19 Vaccine that uses Tris buffer and COMIRNATY (COVID-19 Vaccine, mRNA) that uses Tris buffer can be used interchangeably, as described above, without presenting any safety or effectiveness concerns.As described below under *Product Description*, the formulations that use Tris and PBS buffers, which are covered by this authorization for use in individuals 12 years of age and older, contain the same modRNA and lipids, and the same quantity of these ingredients, per 0.3 mL dose. The two formulations differ with respect to certain inactive ingredients only and have been shown to be analytically comparable.[23] Accordingly, under this

[23] Analytical comparability assessments use laboratory testing to demonstrate that a change in product formulation does not impact a product's safety or effectiveness. For the Pfizer-BioNTech COVID-19 Vaccine, multiple different release parameters were evaluated to assess the comparability of the modified formulation (the formulation with the Tris buffer) to the originally-authorized formulation (the formulation with the PBS buffer). These release parameters ranged from product appearance to size of the lipid-nanoparticle to the integrity of the modRNA in the product. Release and characterization tests include tests for purity, composition, and critical attributes of mRNA

EUA, for individuals 12 years of age and older, the two formulations of COMIRNATY (COVID-19 Vaccine, mRNA) and the two formulations of the Pfizer-BioNTech COVID-19 Vaccine, when prepared according to their respective instructions for use, can be used interchangeably without presenting any safety or effectiveness concerns.

Therefore, for individuals 12 years of age and older, COMIRNATY (COVID-19 Vaccine, mRNA) is authorized to complete the primary regimen or provide a booster dose for individuals who received their initial primary dose(s) with the Pfizer-BioNTech COVID-19 Vaccine, and the Pfizer-BioNTech COVID-19 Vaccine is authorized to complete the primary regimen or provide a booster for individuals who received their initial primary dose(s) with COMIRNATY (COVID-19 Vaccine, mRNA).

Product Description[24]

The Pfizer-BioNTech COVID-19 Vaccine, supplied in two formulations, is provided in three different color-coded multiple dose vials:

	Vials with purple caps	**Vials with gray caps and labels with gray borders**	**Vials with orange caps and labels with orange borders**
Authorized age	12 years of age and older	12 years of age and older	5 through 11 years of age
Formulated to provide	0.3 mL doses, after dilution (each containing 30 µg modRNA)	0.3 mL doses (each containing 30 µg modRNA)	0.2 mL doses, after dilution (each containing 10 µg modRNA)
Buffer used	PBS	Tris	Tris
Dilution	Dilute with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP	Not to be diluted	Dilute with 1.3 mL of sterile 0.9% Sodium Chloride Injection, USP

associated with the activity of the vaccine. The combination of release testing and characterization testing demonstrated that the modified formulation is analytically comparable to the original formulation.

[24] For COMIRNATY (COVID-19 Vaccine, mRNA) that uses the PBS buffer product description, please see the COMIRNATY (COVID-19 Vaccine, mRNA) prescribing information, found here: *https://www.fda.gov/media/151707/download*; for COMIRNATY (COVID-19 Vaccine, mRNA) that uses the Tris buffer product description, please see the COMIRNATY (COVID-19 Vaccine, mRNA) prescribing information, found here: *https://www.fda.gov/media/154834/download.*

Multiple dose vials with purple caps

Each 0.3 mL dose of the Pfizer-BioNTech COVID-19 Vaccine contains 30 µg of modRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2. Each dose of the Pfizer-BioNTech COVID-19 Vaccine also includes the following ingredients: lipids (0.43 mg (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.05 mg 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol), 0.01 mg potassium chloride, 0.01 mg monobasic potassium phosphate, 0.36 mg sodium chloride, 0.07 mg dibasic sodium phosphate dihydrate, and 6 mg sucrose. The Pfizer-BioNTech COVID-19 Vaccine does not contain a preservative. The diluent (0.9% Sodium Chloride Injection) contributes an additional 2.16 mg sodium chloride per dose.

Multiple dose vials with gray caps and labels with gray borders

Each 0.3 mL dose of the Pfizer-BioNTech COVID-19 Vaccine contains 30 µg of a modRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2. Each dose of the Pfizer-BioNTech COVID-19 Vaccine also includes the following ingredients: lipids (0.43 mg (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.05 mg 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.19 mg cholesterol), 0.06 mg tromethamine, 0.4 mg tromethamine hydrochloride, and 31 mg sucrose. The Pfizer-BioNTech COVID-19 Vaccine does not contain a preservative.

Multiple dose vials with orange caps and labels with orange borders

Each 0.2 mL dose of the Pfizer-BioNTech COVID-19 Vaccine contains 10 µg of a modRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2. Each dose of the Pfizer-BioNTech COVID-19 Vaccine also includes the following ingredients: lipids (0.14 mg (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.02 mg 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 0.03 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.06 mg cholesterol), 10.3 mg sucrose, 0.02 mg tromethamine, and 0.13 mg tromethamine hydrochloride. The Pfizer-BioNTech COVID-19 Vaccine does not contain a preservative. The diluent (0.9% Sodium Chloride Injection, USP) contributes 0.9 mg sodium chloride per dose.

The manufacture of the authorized Pfizer-BioNTech COVID-19 Vaccine is limited to those facilities identified and agreed upon in Pfizer's request for authorization.

The Pfizer-BioNTech COVID-19 Vaccine vial label and carton labels are clearly marked for "Emergency Use Authorization." The Pfizer-BioNTech COVID-19 Vaccine is authorized to be distributed, stored, further redistributed, and administered by emergency response stakeholders when packaged in the authorized manufacturer packaging (i.e., vials and cartons), despite the fact that the vial and carton labels may not contain information that otherwise would be required under the FD&C Act.

Pfizer-BioNTech COVID-19 Vaccine is authorized for emergency use with the following product-specific information required to be made available to vaccination providers and recipients, respectively (referred to as "authorized labeling"):

- Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers): Emergency Use Authorization (EUA) of Pfizer-BioNTech COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19) - For 12 Years of Age and Older Dilute Before Use
- Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers): Emergency Use Authorization (EUA) of Pfizer-BioNTech COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19) - For 12 Years of Age and Older Do Not Dilute
- Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers): Emergency Use Authorization (EUA) of Pfizer-BioNTech COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19) - For 5 Through 11 Years of Age Dilute Prior To Use
- Vaccine Information Fact Sheet for Recipients and Caregivers About COMIRNATY (COVID-19 Vaccine, mRNA) and Pfizer-BioNTech COVID-19 Vaccine to Prevent Coronavirus Disease (COVID-19) For Use in Individuals 12 Years of Age and Older
- Vaccine Information Fact Sheet for Recipients and Caregivers About the Pfizer-BioNTech COVID-19 Vaccine to Prevent Coronavirus Disease (COVID-19) for Use in Individuals 5 Through 11 Years of Age

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine,[25] when used to prevent COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh its known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine may be effective in preventing COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that Pfizer-BioNTech COVID-19 Vaccine (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of Pfizer-BioNTech COVID-19 Vaccine under this EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), Pfizer-BioNTech COVID-19 Vaccine is authorized to prevent COVID-19 as described in

[25] The conclusions supporting authorization stated in this section (Section II) also apply to COMIRNATY (COVID-19 Vaccine, mRNA).

the Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

Pfizer Inc. and Authorized Distributor(s)

A. Pfizer Inc. and authorized distributor(s) will ensure that the authorized Pfizer-BioNTech COVID-19 Vaccine is distributed, as directed by the U.S. government, including CDC and/or other designee, and the authorized labeling (i.e., Fact Sheets) will be made available to vaccination providers, recipients, and caregivers consistent with the terms of this letter.

B. Pfizer Inc. and authorized distributor(s) will ensure that appropriate storage and cold chain is maintained until delivered to emergency response stakeholders' receipt sites.

C. Pfizer Inc. will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., emergency response stakeholders, authorized distributors, and vaccination providers) involved in distributing or receiving authorized Pfizer-BioNTech COVID-19 Vaccine. Pfizer Inc. will provide to all relevant stakeholders a copy of this letter of authorization and communicate any subsequent amendments that might be made to this letter of authorization and its authorized labeling.

D. Pfizer Inc. may develop and disseminate instructional and educational materials (e.g., video regarding vaccine handling, storage/cold-chain management, preparation, disposal) that are consistent with the authorized emergency use of the vaccine as described in the letter of authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet public health needs during an emergency. Any instructional and educational materials that are inconsistent with the authorized labeling are prohibited.

E. Pfizer Inc. may request changes to this authorization, including to the authorized Fact Sheets for the vaccine. Any request for changes to this EUA must be submitted to Office of Vaccines Research and Review (OVRR)/Center for Biologics Evaluation and Research (CBER). Such changes require appropriate authorization prior to implementation.[26]

[26] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), or (7), review and concurrence is required from the Preparedness and Response Team (PREP)/Office of the Center Director (OD)/CBER and the Office of Counterterrorism and Emerging Threats (OCET)/Office of the Chief Scientist (OCS).

F. Pfizer Inc. will report to Vaccine Adverse Event Reporting System (VAERS):
- Serious adverse events (irrespective of attribution to vaccination);
- Cases of Multisystem Inflammatory Syndrome in children and adults; and
- Cases of COVID-19 that result in hospitalization or death, that are reported to Pfizer Inc.

These reports should be submitted to VAERS as soon as possible but no later than 15 calendar days from initial receipt of the information by Pfizer Inc.

G. Pfizer Inc. must submit to Investigational New Drug application (IND) number 19736 periodic safety reports at monthly intervals in accordance with a due date agreed upon with the Office of Biostatistics and Epidemiology (OBE)/CBER beginning after the first full calendar month after authorization. Each periodic safety report is required to contain descriptive information which includes:
- A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest;
- A narrative summary and analysis of vaccine administration errors, whether or not associated with an adverse event, that were identified since the last reporting interval;
- Newly identified safety concerns in the interval; and
- Actions taken since the last report because of adverse experiences (for example, changes made to Healthcare Providers Administering Vaccine (Vaccination Providers) Fact Sheet, changes made to studies or studies initiated).

H. No changes will be implemented to the description of the product, manufacturing process, facilities, or equipment without notification to and concurrence by FDA.

I. All manufacturing facilities will comply with Current Good Manufacturing Practice requirements.

J. Pfizer Inc. will submit to the EUA file Certificates of Analysis (CoA) for each drug product lot at least 48 hours prior to vaccine distribution. The CoA will include the established specifications and specific results for each quality control test performed on the final drug product lot.

K. Pfizer Inc. will submit to the EUA file quarterly manufacturing reports, starting in July 2021, that include a listing of all drug substance and drug product lots produced after issuance of this authorization. This report must include lot number, manufacturing site, date of manufacture, and lot disposition, including those lots that were quarantined for investigation or those lots that were rejected. Information on the reasons for lot quarantine or rejection must be included in the report.

L. Pfizer Inc. and authorized distributor(s) will maintain records regarding release of Pfizer-BioNTech COVID-19 Vaccine for distribution (i.e., lot numbers, quantity, release date).

M. Pfizer Inc. and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

N. Pfizer Inc. will conduct post-authorization observational studies to evaluate the association between Pfizer-BioNTech COVID-19 Vaccine and a pre-specified list of adverse events of special interest, including myocarditis and pericarditis, along with deaths and hospitalizations, and severe COVID-19. The study population should include individuals administered the authorized Pfizer-BioNTech COVID-19 Vaccine under this EUA in the general U.S. population (5 years of age and older), individuals who receive a booster dose, populations of interest such as healthcare workers, pregnant women, immunocompromised individuals, subpopulations with specific comorbidities. The studies should be conducted in large scale databases with an active comparator. Pfizer Inc. will provide protocols and status update reports to the IND 19736 with agreed-upon study designs and milestone dates.

Emergency Response Stakeholders

O. Emergency response stakeholders will identify vaccination sites to receive authorized Pfizer-BioNTech COVID-19 Vaccine and ensure its distribution and administration, consistent with the terms of this letter and CDC's COVID-19 Vaccination Program.

P. Emergency response stakeholders will ensure that vaccination providers within their jurisdictions are aware of this letter of authorization, and the terms herein and any subsequent amendments that might be made to the letter of authorization, instruct them about the means through which they are to obtain and administer the vaccine under the EUA, and ensure that the authorized labeling [i.e., Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) and Vaccine Information Fact Sheet for Recipients and Caregivers] is made available to vaccination providers through appropriate means (e.g., e-mail, website).

Q. Emergency response stakeholders receiving authorized Pfizer-BioNTech COVID-19 Vaccine will ensure that appropriate storage and cold chain is maintained.

Vaccination Providers

R. Vaccination providers will administer the vaccine in accordance with the authorization and will participate and comply with the terms and training required by CDC's COVID-19 Vaccination Program.

S. Vaccination providers will provide the Vaccine Information Fact Sheet for Recipients and Caregivers to each individual receiving vaccination and provide the necessary information for receiving their second dose and/or third dose.

T. Vaccination providers administering the vaccine must report the following information associated with the administration of the vaccine of which they become

aware to VAERS in accordance with the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers):

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome in children and adults
- Cases of COVID-19 that result in hospitalization or death

Complete and submit reports to VAERS online at https://vaers.hhs.gov/reportevent.html. The VAERS reports should include the words "Pfizer-BioNTech COVID-19 Vaccine EUA" in the description section of the report. More information is available at vaers.hhs.gov or by calling 1-800-822-7967. To the extent feasible, report to Pfizer Inc. by contacting 1-800-438-1985 or by providing a copy of the VAERS form to Pfizer Inc.; Fax: 1-866-635-8337.

U. Vaccination providers will conduct any follow-up requested by the U.S government, including CDC, FDA, or other designee, regarding adverse events to the extent feasible given the emergency circumstances.

V. Vaccination providers will monitor and comply with CDC and/or emergency response stakeholder vaccine management requirements (e.g., requirements concerning obtaining, tracking, and handling vaccine) and with requirements concerning reporting of vaccine administration data to CDC.

W. Vaccination providers will ensure that any records associated with this EUA are maintained until notified by FDA. Such records will be made available to CDC, and FDA for inspection upon request.

Conditions Related to Printed Matter, Advertising, and Promotion

X. All descriptive printed matter, advertising, and promotional material, relating to the use of the Pfizer-BioNTech COVID-19 Vaccine shall be consistent with the authorized labeling, as well as the terms set forth in this EUA, and meet the requirements set forth in Section 502(a) and (n) of the FD&C Act and FDA implementing regulations.

Y. All descriptive printed matter, advertising, and promotional material relating to the use of the Pfizer-BioNTech COVID-19 Vaccine clearly and conspicuously shall state that:

- This product has not been approved or licensed by FDA, but has been authorized for emergency use by FDA, under an EUA to prevent Coronavirus Disease 2019 (COVID-19) for use either in individuals 12 years of age and older, or in individuals 5 through 11 years of age, as appropriate; and
- The emergency use of this product is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of the medical product under Section 564(b)(1) of the FD&C Act unless the declaration is terminated or authorization revoked sooner.

Condition Related to Export

Z. If the Pfizer-BioNTech COVID-19 Vaccine is exported from the United States, conditions C, D, and O through Y do not apply, but export is permitted only if 1) the regulatory authorities of the country in which the vaccine will be used are fully informed that this vaccine is subject to an EUA and is not approved or licensed by FDA and 2) the intended use of the vaccine will comply in all respects with the laws of the country in which the product will be used. The requirement in this letter that the authorized labeling (i.e., Fact Sheets) be made available to vaccination providers, recipients, and caregivers in condition A will not apply if the authorized labeling (i.e., Fact Sheets) are made available to the regulatory authorities of the country in which the vaccine will be used.

Conditions With Respect to Use of Licensed Product

AA. COMIRNATY (COVID-19 Vaccine, mRNA) is licensed for individuals 16 years of age and older. There remains, however, a significant amount of Pfizer-BioNTech COVID-19 Vaccine that was manufactured and labeled in accordance with this emergency use authorization. The authorization remains in place with respect to the Pfizer-BioNTech COVID-19 Vaccine for this population.

BB. This authorization also covers the use of the licensed COMIRNATY (COVID-19 Vaccine, mRNA) product when used to provide: (1) a two-dose primary regimen for individuals 12 through 15 years of age;[27] (2) a third primary series dose to individuals 12 years of age or older who have undergone solid organ transplantation or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise; (3) a single booster dose after completing the primary series to individuals 16 years of age or older; and (4) a heterologous booster dose in individuals 18 years of age and older who have completed primary vaccination with a different authorized COVID-19 vaccine as described in the Scope of Authorization (Section II) under this EUA. Conditions A through W in this letter apply when COMIRNATY (COVID-19 Vaccine, mRNA) is provided for the uses described in this subsection III.BB., except that product manufactured and labeled in accordance with the approved BLA is deemed to satisfy the manufacturing, labeling, and distribution requirements of this authorization.

[27] As noted above, this includes the first dose of a two-dose primary regimen for individuals who are 11 years old and will turn 12 years of age between their first and second dose in the primary regimen.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

--/S/--

Jacqueline A. O'Shaughnessy, Ph.D.
Acting Chief Scientist
Food and Drug Administration

Enclosures

Exhibit 6

U.S. FOOD & DRUG ADMINISTRATION

August 5, 2020

To: Manufacturers of Surgical Masks;
Health Care Personnel;
Hospital Purchasing Departments;
Authorized Distributors and Authorized Importers; and
Any Other Stakeholders

The U.S. Food and Drug Administration (FDA) is issuing this Emergency Use Authorization (EUA) in response to concerns relating to the insufficient supply and availability of disposable, single-use surgical masks[1,2] (hereafter also referred to as "surgical masks") for use in healthcare settings by health care personnel (HCP)[3] as personal protective equipment (PPE)[4] to provide a physical barrier to fluids and particulate materials to prevent HCP exposure to respiratory droplets and large particles during surgical mask shortages resulting from the Coronavirus Disease 2019 (COVID-19) pandemic, pursuant to section 564 of the Federal, Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3).

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes COVID-19.[5]

---

[1] A surgical mask is a mask that covers the user's nose and mouth and provides a physical barrier to fluids and particulate materials. Surgical masks are generally regulated by FDA as Class II devices under 21 CFR 878.4040 – Surgical apparel.

[2] FDA-cleared surgical face masks, non-surgical face masks, surgical masks with antimicrobial/antiviral agent, and all particulate filtering facepiece respirators are not within the scope of this authorization.

[3] For the purposes of this EUA, HCP refers to all paid and unpaid persons serving in healthcare settings who have the potential for direct or indirect exposure to patients or infectious materials, including body substances (e.g., blood, tissue, and specific body fluids); contaminated medical supplies, devices, and equipment; contaminated environmental surfaces; or contaminated air. These HCP include, but are not limited to, emergency medical service personnel, nurses, nursing assistants, physicians, technicians, therapists, phlebotomists, pharmacists, dentists and dental hygienists, students and trainees, contractual staff not employed by the healthcare facility, and persons not directly involved in patient care, but who could be exposed to infectious agents that can be transmitted in the healthcare setting (e.g., clerical, dietary, environmental services, laundry, security, engineering and facilities management, administrative, billing, and volunteer personnel).

[4] Surgical masks may be effective in blocking splashes and large particle droplets. While surgical masks are not protective against smaller airborne particulates as described in Section II, they are considered PPE because they are intended to be used to protect HCP from infectious disease hazards. Surgical masks are different from non-surgical face masks, which are only used as source control by the general public and are not considered PPE.

[5] U.S. Department of Health and Human Services, Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3. 85 FR 7316 (February 7, 2020).

Pursuant to Section 564 of the Act, and on the basis of such determination, the Secretary of HHS then declared on March 24, 2020, that circumstances exist justifying the authorization of emergency use of medical devices, including alternative products used as medical devices, due to shortages during the COVID-19 pandemic, subject to the terms of any authorization issued under that section.[6]

As discussed further below, I have concluded that a surgical mask meeting the criteria set forth in Section II meets the criteria for issuance of an EUA under Section 564(c) of the Act.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of surgical masks that meet the criteria set forth in Section II pursuant to the Conditions of Authorization (Section IV) of this letter (referred to in this letter as "authorized surgical masks"). Authorized surgical masks will be added to this letter of authorization in Appendix A, as described in the Scope of Authorization (Section II).

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of authorized surgical masks as described in the Scope of Authorization (Section II) of this letter for use in healthcare settings by HCP as PPE during the COVID-19 pandemic meets the criteria for issuance of an authorization under Section 564(c) of the Act, because I have concluded that:

1. SARS-CoV-2, the virus that causes COVID-19, can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that the authorized surgical masks may be effective for use in healthcare settings by HCPs as PPE to provide a physical barrier to fluids and particulate materials to prevent HCP exposure to respiratory droplets and large particles during surgical mask shortages resulting from the COVID-19 pandemic, and that the known and potential benefits of the authorized surgical masks, when used consistent with the scope of this authorization (Section II), outweigh the known and potential risks of such product; and

3. There is no adequate, approved, and available alternative to the emergency use of these authorized surgical masks for use in healthcare settings by HCP to prevent HCP exposure to respiratory droplets and large particles during surgical mask shortages resulting from the COVID-19 pandemic.[7,8]

---

[6] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 17335 (March 27, 2020).

[7] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.

[8] There are not sufficient quantities of surgical masks to meet the needs of the U.S. healthcare system. These articles of PPE are an integral part of patient care during the COVID-19 pandemic. Providing authorization for the introduction into interstate commerce of surgical masks by manufacturers, including those that do not customarily engage in the manufacture of medical devices, helps meet the needs of the healthcare system. Providing HCP who

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited to the use of the authorized surgical masks, for use in healthcare settings by HCP as PPE to provide a physical barrier to fluids and particulate materials to prevent HCP exposure to respiratory droplets and large particles during surgical mask shortages resulting from the COVID-19 pandemic.

Surgical masks are not intended to replace the need for FDA-cleared surgical masks or FDA-cleared or authorized respirators. Surgical masks may be effective in blocking splashes and large-particle droplets; however, because of the loose fit between the surface of the surgical mask and the user's face, leakage can occur around the edge of the mask when the user inhales. Therefore, a surgical mask may not provide the user with a reliable level of protection from inhaling smaller airborne particles and is not considered respiratory protection. For this reason, surgical masks are not recommended for use in aerosol generating procedures and any clinical conditions where there is significant risk of infection through inhalation exposure. In such clinical conditions, a filtering facepiece respirator (such as an N95 respirator) with a tight fit is recommended to provide a more reliable level of respiratory protection against pathogenic biologic airborne particulates.

Authorized Surgical Masks

Surgical masks that have been designed, evaluated, and validated consistent with the following performance criteria and that are not excluded, are authorized for the above-described intended use. The following surgical masks are excluded from the scope and are not authorized under this EUA: (1) surgical masks that are FDA-cleared; (2) surgical masks that are manufactured in China; and (3) surgical masks that include drugs, biologics, nanoparticles, or antimicrobial/antiviral agents. A surgical mask that is not excluded is authorized if it meets the following performance criteria:

- Fluid resistance requirements (liquid barrier performance) consistent with ASTM F1862: *Standard Test Method for Resistance of Medical Face Masks to Penetration by Synthetic Blood (Horizontal Projection of Fixed Volume at a Known Velocity);* [9]
- Flammability performance consistent with the definition of either a Class 1 or Class 2 textile in 16 CFR Part 1610;

---

are on the forefront of the COVID-19 response with sufficient PPE is necessary in order to reduce the risk of illness in HCP and increase their availability to provide care to affected patients or those suspected of having COVID-19.

[9] For the current edition of the FDA-recognized standard(s) referenced in this document, see the FDA Recognized Consensus Standards Database, available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm. For more information regarding use of consensus standards in regulatory submissions, refer to FDA guidance titled "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/appropriate-use-voluntary-consensus-standards-premarket-submissions-medical-devices.

- Particulate filtration efficiency requirements consistent with ASTM F2100: *Standard Specification for Performance of Materials Used in Medical Face Masks*;
- Air flow resistance (i.e., breathability) requirements with an acceptance criterion of <6 mm H_2O/cm^2 for differential pressure (delta P) testing consistent with ASTM F2100: *Standard Specification for Performance of Materials Used in Medical Face Masks* for those masks composed of 4 or more layers; and
- The materials of manufacture are either (1) non-cytotoxic, non-irritating and non-sensitizing consistent with the recommendations in FDA's guidance, "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process'"[10] or (2) conform to the following biocompatibility standards:
    - ISO 10993-1: *Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process*
    - ISO 10993-5: *Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity*
    - ISO 10993-10: *Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization.*

To be added to Appendix A as an authorized surgical mask under this EUA, the surgical mask must not be excluded and manufacturers must provide test reports that demonstrate that the surgical mask meets the performance criteria above. Manufacturers may request the inclusion of any surgical mask model in Appendix A by submitting a request to FDA with the subject line "Surgical Masks EUA" to CDRH-nondiagnosticEUA-templates@fda.hhs.gov and include the following information, which will allow FDA to confirm that the surgical mask meets the criteria and provide other relevant information:

- Manufacturer contact information, name and address of business, email address, contact information for a U.S. agent (if any), in addition to general information about the device such as the proprietary or brand name, model number (if any);
- A copy of the product labeling;
- An estimate of the number of surgical masks you are planning to market and distribute during the public health emergency;
- A summary of the evidence demonstrating that the surgical mask meets the above criteria, including test reports; and
- A list of authorized distributor(s) and/or authorized importer(s),[11] including contact information (name, address, contact person, phone number, and email).

[10] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-international-standard-iso-10993-1-biological-evaluation-medical-devices-part-1-evaluation-and.

[11] "Authorized Distributor(s)" and "Authorized Importer(s)" are identified by the manufacturer in an EUA submission as an entity allowed to import and/or distribute the device. If the entity distributing the device is also the entity importing the device, the manufacturer should so indicate on the list provided to FDA.

The labeling of the authorized surgical masks must:

- Describe the product as a disposable, single-use surgical mask. The labeling must include a list of the body contacting materials (which does not include any drugs, biologics, nanoparticles, or antimicrobial/antiviral agents);
- State that the product is not intended to replace the need for FDA-cleared surgical masks or FDA-cleared or authorized respirators;
- State that surgical masks are not intended to provide protection against pathogenic biological airborne particulates and are not recommended for use in aerosol generating procedures and any clinical conditions where there is significant risk of infection through inhalation exposure; and
- Not include statements that would misrepresent the product or create an undue risk in light of the public health emergency. For example, the labeling must not include any express or implied claims for: (1) reuse, (2) antimicrobial or antiviral protection or related uses, (3) infection prevention, infection reduction, or related uses, or (4) viral filtration efficiency.

Authorized products must be accompanied by the above required labeling, and in addition, the authorized products must be accompanied by the following information pertaining to the emergency use, which are authorized to be made available to HCPs:

- Fact Sheet for Healthcare Personnel: Emergency Use of Authorized Disposable, Single-Use Surgical Masks During the COVID-19 Pandemic

The manufacturer's labeling (which must meet the labeling requirements specified above) and the fact sheet, are referred to as "authorized labeling."

FDA may remove an authorized surgical mask from Appendix A of this EUA if FDA has reason to believe that the product no longer meets the Scope of Authorization (Section II) or any of the Conditions of Authorization (Section IV). FDA will provide the manufacturer 24 hours advance notice of such removal and may work with the manufacturer to resolve the issue(s) that led to removal of the device(s) from Appendix A. Products that are removed from Appendix A will appear on a list maintained on FDA's website.

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of authorized surgical masks as described within this section (the Scope of Authorization, Section II), outweigh the known and potential risks of such products.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that authorized surgical masks may be effective as described within this section (the Scope of Authorization, Section II), pursuant to Section 564(c)(2)(A) of the Act.

FDA has reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, and concludes that authorized surgical masks (as described in the Scope of Authorization, Section II), meet the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of authorized surgical masks must be consistent with, and may not exceed, the terms of this letter, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section IV). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), surgical masks that are determined to meet the criteria set forth in this section (Section II) are authorized under the terms and conditions of this EUA.

III. Waiver of Certain FDA Requirements

I am waiving applicable current good manufacturing practice requirements, including the quality system requirements under 21 CFR Part 820 with respect to the design, manufacture, packaging, labeling, storage, and distribution of the authorized surgical masks that are used in accordance with this EUA.

IV. Conditions of Authorization

Pursuant to Section 564(e) of the Act, I am establishing the following conditions to this authorization:

Manufacturers of Authorized Products

A. Manufacturers will make authorized products available with the authorized labeling (including the labeling requirements described in Section II). Manufacturers must make available all labeling in English, to each end user facility (e.g., each hospital) that receives the authorized products, and may include the authorized labeling with each individual authorized product.

B. Manufacturers must comply with 21 CFR Part 803, and must have a process in place for reporting adverse events of which they become aware to FDA consistent with 21 CFR Part 803. See FDA's webpage "Medical Device Reporting (MDR): How to Report Medical Device Problems"[12] for additional information concerning reporting requirements under 21 CFR Part 803 and procedures.

C. Manufacturers will ensure that any records associated with this EUA are maintained until otherwise notified by FDA. Such records will be made available to FDA for inspection upon request.

[12] FDA guidance, titled "Medical Device Reporting (MDR): How to Report Medical Device Problems" is available at https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

D. Through a process of inventory control, manufacturers will maintain records of the entities to which they distribute the surgical masks and the numbers of each such product they distribute.

E. Manufacturers will notify FDA of any authorized distributor(s) and/or authorized importers of the authorized surgical masks, including the name, address, and phone number of any authorized distributor(s) and authorized importer(s), and provide authorized distributor(s) and authorized importer(s) with a copy of this EUA and any updates.

F. Manufacturers are authorized to make available additional information relating to the emergency use of the product that is consistent with, and does not exceed, the terms of this letter of authorization.

G. Manufacturers of authorized surgical masks will submit, upon FDA's request, new lots of the authorized surgical masks for testing by FDA or by another entity designated by FDA. The manufacturers must not distribute any lot or shipment that fails testing, meaning the lot or shipment containing a lot that did not perform as expected based on the performance criteria in the Scope of Authorization (Section II). FDA will make the manufacturer aware of the testing results.

Authorized Distributors and Authorized Importers

H. Authorized Distributors and Authorized Importers must ensure that authorized surgical masks comply with condition A of this EUA.

I. Through a process of inventory control, Authorized Distributors and Authorized Importers will maintain records of the entities to which they distribute the surgical masks and how many of each authorized product model they distribute or import, as applicable.

J. Authorized Distributors and Authorized Importers will ensure that any records associated with this EUA are maintained until otherwise notified by FDA. Such records will be made available to FDA for inspection upon request.

K. Authorized Distributors and Authorized Importers of authorized surgical masks will submit, upon FDA's request, lots or shipments of the authorized surgical masks for testing by FDA or by another entity designated by FDA. Authorized Distributors and Authorized Importers must not distribute any lot or shipment that fails testing, meaning the lot or shipment containing a lot that did not perform as expected based on the performance criteria in the Scope of Authorization (Section II). FDA will make the Authorized Distributor or Authorized Importer aware of the testing results.

Conditions Related to Advertising and Promotion

L. All descriptive printed matter, including advertising and promotional materials, relating to the use of the authorized surgical mask shall be consistent with the labeling requirements listed in Section II and this section (Conditions of Authorization) of this EUA, and the applicable requirements set forth in the Act and FDA regulations.

M. No descriptive printed matter, including advertising or promotional materials, relating to the use of the authorized surgical mask may represent or suggest that such product is safe or effective for the prevention or treatment of COVID-19.

N. All descriptive printed matter, including advertising and promotional materials, relating to the use of the product shall clearly and conspicuously state that:

- The product has not been FDA cleared or approved.
- The product has been authorized by FDA under an EUA for use in healthcare settings by HCP as PPE to provide a physical barrier to fluids and particulate materials to prevent HCP exposure to respiratory droplets and large particles during surgical mask shortages resulting from the COVID-19 pandemic.
- This product is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of medical devices, including alternative products used as medical devices, during the COVID-19 outbreak, under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1) unless the authorization is terminated or revoked sooner.

V. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying this authorization is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

Exhibit 7

Evidence for Community Cloth Face Masking to Limit the Spread of SARS-CoV-2: A Critical Review

By Ian T. Liu, Vinay Prasad and Jonathan J. Darrow

November 8, 2021

CATO WORKING PAPER

No. 64

CATO INSTITUTE

Cato Working Papers are intended to circulate research in progress for comment and discussion.

Available at www.cato.org/workingpapers

Evidence for Community Cloth Face Masking to Limit the Spread of SARS-CoV-2: A Critical Review

Ian T. Liu, JD, MS[a]
Vinay Prasad, MD, MPH[b]
Jonathan J. Darrow, SJD, LLM, JD, MBA[c,d*]

[a] University of Colorado Anschutz Medical Campus, Aurora, CO
[b] Department of Epidemiology and Biostatistics, University of California San Francisco
[c] Bentley University, Waltham, MA
[d] Harvard Medical School, Boston, MA

***Corresponding Author:** Dr. Jonathan J. Darrow, 1620 Tremont St., Suite 3030, Boston, MA 02120, 347-792-2246, jjdarrow@bwh.harvard.edu. LLM waived.

Acknowledgments: The authors thank Aaron Kesselheim, Timo Minssen, two anonymous reviewers, and the editors of Regulation for helpful comments.

Disclosures: Dr. Prasad reports grants from Arnold Ventures, royalties from Johns Hopkins University Press and Medscape, honoraria for grand rounds/lectures from universities, medical centers, nonprofits, and professional societies, consulting fees from UnitedHealthcare, speaking fees from eviCore, and funding via Patreon for Plenary Session, a podcast. Dr. Darrow receives research support from Arnold Ventures, the Commonwealth Fund, the Greenwall Foundation, Health Action International's ACCISS program, the Kaiser Permanente Institute for Health Policy, West Health, and under a Novo Nordisk Foundation grant for a scientifically independent Collaborative Research Programme (grant NNF17SA0027784). These funders had no role in the conception, drafting, review, or approval of the manuscript or the decision to submit the manuscript for publication.

Abstract

The use of cloth facemasks in community settings has become an accepted public policy response to decrease disease transmission during the COVID-19 pandemic. Yet evidence of facemask efficacy is based primarily on observational studies that are subject to confounding and on mechanistic studies that rely on surrogate endpoints (such as droplet dispersion) as proxies for disease transmission. The available clinical evidence of facemask efficacy is of low quality and the best available clinical evidence has mostly failed to show efficacy, with fourteen of sixteen identified randomized controlled trials comparing face masks to no mask controls failing to find statistically significant benefit in the intent-to-treat populations. Of sixteen quantitative meta-analyses, eight were equivocal or critical as to whether evidence supports a public recommendation of masks, and the remaining eight supported a public mask intervention on limited evidence primarily on the basis of the precautionary principle. Although weak evidence should not preclude precautionary actions in the face of unprecedented events such as the COVID-19 pandemic, ethical principles require that the strength of the evidence and best estimates of amount of benefit be truthfully communicated to the public.

Keywords: facemasks, health policy, COVID-19, infectious disease, epidemiology, bioethics

Introduction

Until April 2020, World Health Organization COVID-19 guidelines stated that "[c]loth (e.g. cotton or gauze) masks are not recommended under any circumstance,"[1] which were updated in June 2020 to state that "the widespread use of masks by healthy people in the community setting is not yet supported by high quality or direct scientific evidence."[2] In the surgical theater context, a Cochrane review found "no statistically significant difference in infection rates between the masked and unmasked group in any of the trials."[3] Another Cochrane review, of influenza-like-illness, found "low certainty evidence from nine trials (3507 participants) that wearing a mask may make little or no difference to the outcome of influenza-like illness (ILI) compared to not wearing a mask (risk ratio (RR) 0.99, 95% confidence interval (CI) 0.82 to 1.18)."[4]

These observations may come as a surprise to those in countries, such as the United States, where government leaders, news media, and even public health officials have repeatedly asserted that the widespread use of masks will help to prevent transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19. By September 2020, the U.S. federal government had distributed 600 million face masks for use by the public as part of the response to the pandemic.[5,6] At the local level, 32 states and numerous

---

[1] *Advice on the Use of Masks [in] the Community, During Home Care and in Health Care Settings in the Context of the Novel Coronavirus (2019-Ncov) Outbreak: Interim Guidance*, WORLD HEALTH ORG., Jan. 29, 2020, at 2, https://apps.who.int/iris/handle/10665/330987 (last visited Sep. 5, 2021).

[2] *Advice on the Use of Masks in the Context of COVID-19: Interim Guidance*, WORLD HEALTH ORG., June 5, 2020, at 6, https://apps.who.int/iris/handle/10665/332293 (last visited Sep. 5, 2021).

[3] Marina Vincent & Peggy Edwards, *Disposable Surgical Face Masks for Preventing Surgical Wound Infection in Clean Surgery*, 4 COCHRANE DATABASE SYS. REV. 1, 1 (2016).

[4] Tom Jefferson et al., *Physical Interventions to Interrupt or Reduce the Spread of Respiratory Viruses (Review)*, 11 COCHRANE DATABASE SYS. REV. 1, 2 (2020).

[5] Helen Branswell et al., *The Trump Administration Haphazardly Gave Away Millions of Covid-19 Masks — To Schools, Broadcasters, and Large Corporations*, STAT NEWS, Aug. 13, 2020, https://www.statnews.com/2020/08/13/the-trump-administration-haphazardly-gave-away-millions-of-masks-to-schools-broadcasters-and-fortune-500-companies/.

municipalities implemented mask mandates,[7,8] and calls for a nationwide mask mandate garnered significant attention.[9] At the height of the pandemic, New York City instituted a $1000 fine for those who refuse to wear face masks in public,[10] and prominent national leaders stated that "[w]earing masks is not a political statement, it is a scientific imperative."[11] Over 40% of the global population lives in countries that mandate mask-wearing in public areas.[12] As COVID-19 persists, community masking policies continue to be the subject of public health and public attention.

These public statements, official policies, and mask requirements have become politically divisive.[13] Non-partisan, evidence-based decision-making is essential to increasing public confidence in appropriate public health interventions. We review the evidence for aerosol transmission of SARS-CoV-2, the mechanistic evidence of how masks may interrupt transmission of respiratory infections and in particular SARS-CoV-2, and the available clinical evidence of the impact of cloth facemask use in community settings on respiratory infection rates, including by SARS-CoV-2.

---

[6] KHN Morning Briefing, *White House Abandoned HHS Plan to Mail Masks to Every American in April*, KAISER HEALTH NEWS, Sept. 18, 2020, https://khn.org/morning-breakout/white-house-abandoned-hhs-plan-to-mail-masks-to-every-american-in-april/ ("Documents obtained by The Washington Post and NBC News detail the Department of Health and Human Service's proposal to deliver 650 million cloth masks in April."); *id.*("A spokesperson for the Department of Health and Human Services told NBC News that 600 million masks have been distributed . . . .")

[7] *What U.S. States Require Masks in Public?*, #MASKS4ALL, https://masks4all.co/what-states-require-masks/ (last visited Nov. 11, 2020).

[8] Austin L. Wright et al., *Tracking Mask Mandates During the Covid-19 Pandemic*, 104 UNIV. CHI. BECKER FRIEDMAN INST. ECON. WORKING PAPER 1 (2020).

[9] Sheryl G. Stolberg, *Biden's Call for 'National Mask Mandate' Gains Traction in Public Health Circles*. N.Y. TIMES, OCT. 29, 2020, https://www.nytimes.com/2020/10/29/us/politics/trump-biden-mask-mandate.html (last visited Nov. 11, 2020).

[10] Marisa Peñaloza, *New York City Imposes Fines of Up to $1,000 for Those Who Refuse to Wear Face Masks*. NAT. PUB. RADIO, SEP. 30, 2020, https://www.npr.org/sections/coronavirus-live-updates/2020/09/30/918704017/new-york-city-imposes-fines-of-up-to-1-000-for-those-who-refuse-to-wear-face-mas (last visited Nov. 11, 2020).

[11] Reuters, *Biden Says He Would If Elected Mandate Masks in Interstate Transportation*, US NEWS, Oct. 23, 2020, https://www.usnews.com/news/top-news/articles/2020-10-23/biden-says-he-would-if-elected-mandate-masks-in-interstate-transportation (last visited Nov. 11, 2020).

[12] *What Countries Require Masks in Public or Recommend Masks?*, #MASKS4ALL, https://masks4all.co/what-countries-require-masks-in-public/ (last visited May 8, 2021).

[13] Shana K. Gadarian et al., *Partisanship, Health Behavior, and Policy Attitudes in the Early Stages of the COVID-19 Pandemic*, 16 PLOS ONE 1, 1 (2021).

I. Evidence of aerosol transmission of SARS-CoV-2

Airborne diseases can be transmitted from person to person when respiratory secretions containing infectious particles from one person come into contact with the mucosal membranes of another, such as the eyes, nose, or mouth.[14] Such secretions are emitted into the surrounding air when infected individuals cough[15] or sneeze,[16] or even during the events of daily living irrespective of health status,[17] such as breathing,[18] talking,[19,20] or singing.[21]

These activities result in the emission of secretions of all sizes.[22] Larger particles greater than a "critical size" behave ballistically,[23] falling to nearby surfaces within a 1- to 2-meter radius[24,25] (although air currents can allow particles to travel beyond this distance[26,27]), while smaller particles evaporate before falling to the ground.[28] There is no universally accepted threshold delineating these two categories, but by convention droplets are those particles greater

---

[14] Eunice Y. C. Shiu et al., *Controversy Around Airborne Versus Droplet Transmission of Respiratory Viruses: Implication for Infection Prevention*, 32 CURRENT OPINION INFECTIOUS DISEASES 372, 373 (2019).
[15] Jinho Lee et al., *Quantity, Size Distribution, and Characteristics of Cough-Generated Aerosol Produced by Patients with an Upper Respiratory Tract Infection*, 19 AEROSOL AIR QUALITY RESEARCH 840, 840 (2019).
[16] Z. Y. Han et al., *Characterizations of Particle Size Distribution of the Droplets Exhaled by Sneeze*, 10 J. ROY. SOC'Y INTERFACE 1, 2 (2013).
[17] Lidia J. Morawska et al., *Size Distribution and Sites of Origin of Droplets Expelled from the Human Respiratory Tract During Expiratory Activities*, 40 J. AEROSOL SCI. 256, 256 (2009).
[18] G. R. Johnson et al., *Modality of Human Expired Aerosol Size Distributions*, 42 J. AEROSOL SCI. 839, 844 (2011).
[19] Valentyn Stadnytskyi et al., *The Airborne Lifetime of Small Speech Droplets and Their Potential Importance in SARS-CoV-2 Transmission*, 117 PROC. NAT'L ACAD. SCI. 11875, 11875 (2020).
[20] Sima Asadi et al., *Aerosol Emission and Superemission During Human Speech Increase with Voice Loudness*, 9 SCI. REPORTS 1 (2019).
[21] Malin Alsved et al., *Exhaled Respiratory Particles During Singing and Talking*, 54 AEROSOL SCI. & TECH. 1245 (2020).
[22] Lidia J. Morawska et al., *Size Distribution and Sites of Origin of Droplets Expelled from the Human Respiratory Tract During Expiratory Activities*, 40 J. AEROSOL SCI. 256, 256 (2009).
[23] Raymond Tellier et al., *Recognition of Aerosol Transmission of Infectious Agents: A Commentary*, 19 BMC INFECTIOUS DISEASES 1, 2 (2019).
[24] Lidia J. Morawska, *Droplet Fate in Indoor Environments, or Can We Prevent the Spread of Infection?*, *in* Proceedings of Indoor Air 2005: the 10th International Conference on Indoor Air Quality and Climate 9 (2005).
[25] *Infection Prevention and Control of Epidemic- and Pandemic-Prone Acute Respiratory Diseases in Health Care: Interim Guidance*, June 2007, WORLD HEALTH ORG., http://www.who.int/csr/resources/publications/WHO_CDS_EPR_2007_6/en (last visited Nov. 11, 2020).
[26] Talib Dbouk & Dimitris Drikakis, *On Coughing and Airborne Droplet Transmission to Humans*, 32 PHYSICS FLUIDS 053310-1, 053310-7 (2020).
[27] Padmanabha P. Simha & Prasana S. Mohan Rao, *Universal Trends in Human Cough Airflows at Large Distances*, 32 PHYSICS FLUIDS 081905-1, 081905-7 (2020).
[28] Rajat Mittal et al., *The Flow Physics of COVID-19*, 894 J. FLUID MECHANICS F2-1, F2-1 (2020).

than about 10 μm in diameter, while aerosols are those smaller than this size.[29,30] When smaller particles evaporate,[31] they can stay suspended in the air for long periods of time and be inhaled,[32] potentially causing infection deeper in the respiratory tract and at lower concentrations.[33,34] Smaller particles are preferentially generated during higher-velocity respiratory events such as coughing and sneezing, with one study finding that 99.9% of particles emitted by subjects with a cold during coughing were <5 μm in diameter,[35] and another finding that more than 97% of the droplets emitted by healthy volunteers in the study were <1 μm in diameter.[36,37] Exhaled particles <5 μm in diameter have been found to carry the majority of virus in exhaled human breath,[38] and patients with upper respiratory infections emitted significantly greater numbers of particles (5x10^6 compared to 1x10^6, P<0.05) while sick compared to after recovery.[39]

---

[29] Eunice Y. C. Shiu et al., *Controversy Around Airborne Versus Droplet Transmission of Respiratory Viruses: Implication for Infection Prevention*, 32 CURRENT OPINION INFECTIOUS DISEASES 372, 375 (2019).
[30] J. W. Tang et al., *Factors Involved in the Aerosol Transmission of Infection and Control of Ventilation in Healthcare Premises*, 64 J. HOSP. INFECTION MECHANICS 100, 101 (2006).
[31] Lidia J. Morawska, *Droplet Fate in Indoor Environments, or Can We Prevent the Spread of Infection?*, at 9, *in* Proceedings of Indoor Air 2005: the 10th International Conference on Indoor Air Quality and Climate (2005).
[32] Catharyn T. Liverman, *Understanding the Risk to Healthcare Personnel*, at 30, *in* Preventing Transmission of Pandemic Influenza and Other Viral Respiratory Diseases: Personal Protective Equipment for Healthcare Personnel: Update 2010 (2010), https://www.nap.edu/read/13027/chapter/4#30.
[33] James H. Vincent, *Health-Related Aerosol Measurement: A Review of Existing Sampling Criteria and Proposals for New Ones*, 7 J. ENVTL. MONITORING 1037, 1037–38 (2005).
[34] Rachael M. Jones & Lisa M. Brosseau, *Aerosol Transmission of Infectious Disease*, 57 J. OCCUPATIONAL & ENVTL. MED. 501, 502 (2015).
[35] G. R. Johnson GR et al., *Modality of Human Expired Aerosol Size Distributions*, 42 J. AEROSOL SCI. 839, 844 (2011).
[36] Gustavo Zayas et al., *Cough Aerosol in Healthy Participants: Fundamental Knowledge to Optimize Droplet-Spread Infectious Respiratory Disease Management*, 12 BMC PULMONARY MED. 1, 1 (2012).
[37] Shinhao Yang et al., *The Size and Concentration of Droplets Generated by Coughing in Human Subjects*, 20 J. AEROSOL SCI. 484, 484 (2007) (finding that 82% off droplet nuclei exhaled during coughing were between 0.74–2.12 microns in diameter).
[38] Donald K. Milton et al., *Influenza Virus Aerosols in Human Exhaled Breath: Particle Size, Culturability, and Effect of Surgical Masks*, 9 PLOS PATHOGEN 1, 3 (2013).
[39] Jinho Lee et al., *Quantity, Size Distribution, and Characteristics of Cough-Generated Aerosol Produced by Patients with an Upper Respiratory Tract Infection*, 19 AEROSOL AIR QUALITY RESEARCH 840, 846 (2019).

The primary mode of transmission (aerosol vs. droplet) for viral respiratory infections, including SARS-CoV-2, is controversial and remains unclear.[40,41,42,43,44,45] If aerosol transmission plays a substantial role, the ability of masks to serve as a physical barrier to droplets becomes a less reliable surrogate of efficacy, since air expelled from the lungs necessarily penetrates the mask or flows around its edges, potentially advecting aerosols along with it.

Aerosol transmission has been demonstrated or is considered likely for SARS-CoV,[46] Middle East Respiratory Syndrome (MERS),[47] H1N1 influenza,[48] and respiratory syncytial virus,[49] and a growing body of laboratory, animal, and clinical evidence suggests SARS-CoV-2 is also spread via this mechanism.[50,51] One study found SARS-CoV-2 aerosolizes with equal or greater efficiency than both SARS-CoV-1 and MERS-CoV,[52] and retains stability and infectivity for 16 hours in respirable-sized aerosols.[53] Another study found COVID-19 patients exhale

---

[40] Eunice Y. C. Shiu et al., *Controversy Around Airborne Versus Droplet Transmission of Respiratory Viruses: Implication for Infection Prevention*, 32 CURRENT OPINION INFECTIOUS DISEASES 372 (2019).
[41] Mahesh Jayaweera et al., *Transmission of COVID-19 Virus by Droplets and Aerosols: A Critical Review on the Unresolved Dichotomy*, 188 ENVTL. RESEARCH 1 (2020).
[42] Michael Klompas et al., *Airborne Transmission of SARS-CoV-2: Theoretical Considerations and Available Evidence*, 324 J. AM. MED. ASS'N 441 (2020).
[43] Kevin L. Schwartz et al., *Lack of COVID-19 Transmission on an International Flight*, 192 CAN. MED. ASS'N J. E410 (2020).
[44] Jan Gralton et al., *The Role of Particle Size in Aerosolised Pathogen Transmission: A Review*, 62 J. INFECTION 1 (2011).
[45] Raymond Tellier, *Aerosol Transmission of Influenza A Virus: A Review of New Studies*, 6 J. ROYAL SOC'Y INTERFACE S783 (2009).
[46] Ignatius T. Yu et al., *Evidence of Airborne Transmission of the Severe Acute Respiratory Syndrome Virus*, 350 NEW ENG. J. MED. 1731, 1731 (2004).
[47] Shenlang Xiao et al., *A Study of the Probable Transmission Routes of MERS-CoV During the First Hospital Outbreak in the Republic of Korea*, 28 INDOOR AIR 51, 51 (2018).
[48] Hogna Zhang et al., *Airborne Spread and Infection of a Novel Swine-Origin Influenza a (H1N1) Virus*, 10 VIROLOGY J. 1, 1 (2013).
[49] Hemant Kulkarni et al., *Evidence of Respiratory Syncytial Virus Spread by Aerosol. Time to Revisit Infection Control Strategies?* 194 AM. J. RESPIRATORY & CRITICAL CARE MED. 308, 308 (2016).
[50] Elizabeth L. Anderson et al., *Consideration of the Aerosol Transmission for COVID-19 and Public Health*, 40 RISK ANALYSIS 902, 902 (2020).
[51] Song Tang et al., *Aerosol Transmission of SARS-CoV-2? Evidence, Prevention and Control*, 144 ENVT. INT'L 1, 1 (2020).
[52] Alyssa C. Fears et al., *Persistence of Severe Acute Respiratory Syndrome Coronavirus 2 in Aerosol Suspensions*, 26 EMERGING INFECTIOUS DISEASES INT'L 2168, 2170 (2020).
[53] Neeltje Van Doremalen et al., *Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1*, 382 NEW ENG. J. MED. 1564, 1565 (2020).

millions of SARS-CoV-2 copies into the surrounding air every hour.[54] Even in the early stages of the illness when coughing or sneezing are uncommon, infectious SARS-CoV-2 aerosols have been found in air samples taken at the foot of patient beds in clinical settings.[55] SARS-CoV-2 viral particles have been detected in low-touch areas (e.g. under beds and on unused window ledges) consistent with sustained aerosol distribution, as well as in most (58%) of air samples taken from hallways outside patient rooms.[56] Evidence of transmission before patients become symptomatic suggests coughing and sneezing are not essential,[57,58,59,60] tending to partially undermine the importance of video evidence showing reductions in droplet dispersion when individuals cough through masks. Observational evidence of 110 SARS-CoV-2 cases in 11 clusters found transmission rates of COVID-19 that were more than 18 times higher in closed environments, where aerosols can more easily remain concentrated, than in open-air environments.[61] In one published report, an index patient often passed by the open door of the secondary patient's apartment—but never went inside.[62]

---

[54] Jianxin Ma et al., *COVID-19 Patients in Earlier Stages Exhaled Millions of SARS-CoV-2 per Hour*, 72 CLINICAL INFECTIOUS DISEASES e652, e653 (2021).
[55] Joshua L. Santarpia et al., *The Size and Culturability of Patient-Generated SARS-CoV-2 Aerosol*, J. EXPOSURE SCI. & ENVTL. EPIDEMIOLOGY 1, 2 (2020).
[56] Joshua L. Santarpia et al., *Aerosol and Surface Contamination of SARS-CoV-2 Observed in Quarantine and Isolation Care*, 10 SCI. REPORTS 1, 3 (2020).
[57] Nathan W. Furukawa et al., *Evidence Supporting Transmission of Severe Acute Respiratory Syndrome Coronavirus 2 While Presymptomatic or Asymptomatic*, 26 EMERGING INFECTIOUS DISEASES e1, e1 (2020).
[58] Kenji Mizumoto et al., *Estimating the Asymptomatic Proportion of Coronavirus Disease 2019 (COVID-19) Cases on Board the Diamond Princess Cruise Ship, Yokohama, Japan, 2020*, 25 EUROSURVEILLANCE 1, 3–4 (2020).
[59] Daniel P. Oran et al., *Prevalence of Asymptomatic SARS-Cov-2 Infection: A Narrative Review*, 173 ANNALS INTERNAL MED. 362, 365–66 (2020).
[60] Seyed M. Moghadas et al., *The Implications of Silent Transmission for the Control of COVID-19 Outbreaks,* 117 PROCEEDINGS NAT'L ACAD. SCI. 17513 (2020).
[61] Hiroshi Nishiura et al., *Closed Environments Facilitate Secondary Transmission of Coronavirus Disease 2019 (COVID-19)*, MEDRXIV 1, 2 (2020).
[62] Juan Wang & Guoqiang Du, *COVID-19 May Transmit Through Aerosol*, 189 IRISH J. MED. SCI. 1143, 1143 (2020).

Certain "super-spreader" events also suggest that aerosols serve as an important mode of transmission for SARS-CoV-2.[63,64,65,66] For example, a single index patient at a restaurant in Guangzhou, China infected 4 people sitting at his own table, and 5 strangers sitting at adjacent tables up to 4.6 meters (15 feet) away with whom video evidence confirmed that no close contact was shared.[67] One ward of a Dutch nursing home reported 34 cases (17 of 21 residents; 17 of 34 workers)—despite mask-wearing requirements for healthcare workers and residents' limited mobility—in a week where the Netherlands recorded only 493 cases total; the authors isolated SARS-CoV-2 RNA in living room air conditioners and concluded that transmission was likely due to aerosol transmission and recirculation of contaminated air.[68] At a choir rehearsal in Skagit Valley, Washington, a single infected individual spread SARS-CoV-2 to 53 of 59 attendees—a pattern some have concluded is suggestive of aerosol transmission.[69] Super-spreader events could also be explained by transmission via door handles or other fomites,[70] but substantially higher rates of SARS-CoV-2 positivity have been found in exhaled breath samples (26.9%) than in either indoor air samples (3.8%) or surfaces such as cell phones, floors, and computer

---

[63] Lidia Morawska & Donald K. Milton, *It Is Time to Address Airborne Transmission of Coronavirus Disease 2019 (COVID-19)*, 71 CLINICAL INFECTIOUS DISEASES 2311 (2020).
[64] *Rapid Expert Consultation on the Possibility of Bioaerosol Spread of SARS-CoV-2 for the COVID-19 Pandemic (April 1, 2020)*, at 3, NAT'L ACADS. OF SCIS., ENG'G, & MED., Washington, DC: The National Academies Press (2020), https://www.nap.edu/catalog/25769/rapid-expert-consultation-on-the-possibility-of-bioaerosol-spread-of-sars-cov-2-for-the-covid-19-pandemic-april-1-2020 (last visited Sep. 5, 2021).
[65] Kevin P. Fennelly, *Particle Sizes of Infectious Aerosols: Implications for Infection Control*, 8 LANCET RESPIRATORY MED. 914, 917–20 (2020).
[66] *Coronavirus Disease 2019 (COVID-19)*, CENTERS FOR DISEASE CONTROL & PREVENTION, https://www.cdc.gov/coronavirus/2019-ncov/faq.html (last visited Oct. 21, 2020).
[67] Yuguo Li et al., *Probable Airborne Transmission of SARS-CoV-2 in a Poorly Ventilated Restaurant*, 196 BLDG. & ENVT. 1, 2–3 (2021).
[68] Peter de Man P et al., *Outbreak of Coronavirus Disease 2019 (COVID-19) in a Nursing Home Associated with Aerosol Transmission as a Result of Inadequate Ventilation*, 73 CLINICAL INFECTIOUS DISEASES 170, 171 (2020).
[69] Shelly L. Miller et al., *Transmission of SARS-CoV-2 by Inhalation of Respiratory Aerosol in the Skagit Valley Chorale Superspreading Event*, 31 INDOOR AIR 314, 315–316 (2021).
[70] Michael Klompas et al., *Airborne Transmission of SARS-CoV-2: Theoretical Considerations and Available Evidence*, 324 J. AM. MED. ASS'N 441, 441 (2020).

keyboards (5.4%).[71] A non-clinical study also supported the conclusion that SARS-CoV-2 is transmitted primarily via droplets or aerosols rather than via fomites, based on transmission to all exposed uninfected hamsters when placed in cages separated by 1.8 cm from cages with infected hamsters that shared a common air supply for 8 hours, but to only 1 of 3 uninfected hamsters exposed one-at-a-time for 48 hours to soiled cages (i.e., fomites).[72]

II. Mechanistic evidence of facemask effectiveness

Much of the evidence supporting public mask wearing is based on the surrogate endpoint of droplet dispersion, reductions in which are hypothesized to correlate with reductions in disease transmission. This intuition is based on the ability of masks—and indeed any sufficiently dense object or material—to act as a physical barrier that reduces the volume of larger respiratory secretions that are projected directly forward from the mask wearer, or the distance that those droplets travel,[73,74] and a robust literature exists documenting the filtration qualities of the various fabrics used to construct face masks.[75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93]

---

[71] Jianxin Ma et al., *COVID-19 Patients in Earlier Stages Exhaled Millions of SARS-CoV-2 per Hour*, 72 CLINICAL INFECTIOUS DISEASES e652, e653 (2021).
[72] Sin F. Sia et al., *Pathogenesis and Transmission of SARS-CoV-2 in Golden Hamsters*, 583 NATURE 834, 836 (2020).
[73] Lucia Bandiera et al., *Face Coverings and Respiratory Tract Droplet Dispersion*, 7 ROYAL SOC'Y OPEN SCI. 1, 6 (2020).
[74] Hiroshi Ueki et al., *Effectiveness of Face Masks in Preventing Airborne Transmission of SARS-CoV-2*, 5 MSPHERE 1 (2020).
[75] Alex Rodriguez-Palacios et al., *Textile Masks and Surface Covers—A Spray Simulation Method and a "Universal Droplet Reduction Model" Against Respiratory Pandemics*, 7 FRONTIERS MED. 1 (2020).
[76] Qing-Xia Ma et al., *Potential Utilities of Mask-Wearing and Instant Hand Hygiene for Fighting SARS-CoV-2*, 92 J. MED. VIROLOGY 1567 (2020).
[77] Kenneth D. Long KD et al., *Measurement of Filtration Efficiencies of Healthcare and Consumer Materials Using Modified Respirator Fit Tester Setup*, 15 PLOS ONE 1 (2020).
[78] Eugenia O'Kelly et al., *Ability of Fabric Face Mask Materials to Filter Ultrafine Particles at Coughing Velocity*, 10 BMJ OPEN 1 (2020).
[79] Weixing Hao et al., *Filtration Performances of Non-medical Materials as Candidates for Manufacturing Facemasks and Respirators*, 229 INT'L J. HYGIENE & ENVTL. HEALTH 1 (2020).
[80] Masayoshi Furuhashi, *A Study on the Microbial Filtration Efficiency of Surgical Face Masks—With Special Reference to the Non-woven Fabric Mask*, 25 BULL. TOKYO MED. & DENTAL UNIV. 7 (1978).
[81] Saraswati A. Rizki & Andree Kurniawan, *Efficacy of Cloth Face Mask in Reducing COVID-19 Transmission: A Literature Review*, 1 KESMAS NAT'L PUB. HEALTH J. 43 (2020).

Such studies examine the ability of fabric to filter particles as they pass through—rather than around—mask material. If aerosols can cause infection, however, then filtering capability is unlikely to be reliable surrogate for infection control, since exhaled air necessarily either leaks around a mask's edges or passes through it.[94,95,96] Such leakage has been shown to account for the vast majority (~5:1 ratio) of particle penetration of standardized surgical masks,[97] and exhaled air easily passes around the edges of most cloth masks.[98,99,100,101,102] One study of cloth

---

[82] Onur Aydin et al., *Performance of Fabrics for Home-Made Masks Against the Spread of COVID-19 Through Droplets: A Quantitative Mechanistic Study*, 40 EXTREME MECHANICS LETTERS 1 (2020).
[83] Mervin Zhao et al., *Materials Selection for Homemade Cloth Face Coverings and Their Filtration Efficiency Enhancement with Triboelectric Charging*, 20 NANO LETTERS 5544 (2020).
[84] Adam F. Parlin et al., *A Laboratory-Based Study Examining the Properties of Silk Fabric to Evaluate Its Potential as a Protective Barrier for Personal Protective Equipment and as a Functional Material for Face Coverings During the COVID-19 Pandemic*, 15 PLOS ONE 1 (2020).
[85] Lukas Maurer et al., *Community Masks During the SARS-CoV-2 Pandemic: Filtration Efficacy and Air Resistance*, 34 J. AEROSOL MED. & PULMONARY DRUG DELIVERY 1 (2021).
[86] Harriet Whiley et al., *Viral Filtration Efficiency of Fabric Masks Compared With Surgical and N95 Masks*, 9 PATHOGENS 1 (2020).
[87] Samy Rengasamy et al., *Simple Respiratory Protection–Evaluation of the Filtration Performance of Cloth Masks and Common Fabric Materials Against 20–1000 nm Size Particles*, 54 ANNALS OCCUPATIONAL HYGIENE 789 (2010).
[88] Christopher D. Zangmeister et al., *Filtration Efficiencies of Nanoscale Aerosol by Cloth Mask Materials Used To Slow the Spread of SARS-CoV-2*, 14 ACS NANO 9188 (2020).
[89] Tara Oberg & Lisa M. Brosseau, *Surgical Mask Filter and Fit Performance*, 36 AM. J. INFECTION CONTROL 276 (2008).
[90] Jasper F. Chan et al., *Surgical Mask Partition Reduces the Risk of Non-contact Transmission in a Golden Syrian Hamster Model for Coronavirus Disease 2019 (COVID-19)*, 71 CLINICAL INFECTIOUS DISEASES 2139, 2139 (2021).
[91] Laura H. Kwong et al., *Review of the Breathability and Filtration Efficiency of Common Household Materials for Face Masks*, 15 ACS NANO 5904 (2021).
[92] Ashish Sharma et al., *Efficacy of Facemasks in Mitigating Respiratory Exposure to Submicron Aerosols*, 422 J. HAZARDOUS MATERIALS 1 (2022).
[93] Monica Gandhi & Linsey C. Marr, *Uniting Infectious Disease and Physical Science Principles on the Importance of Face Masks for COVID-19*, 2 MED 29, 30 (2021).
[94] Michael Klompas et al., *Airborne Transmission of SARS-CoV-2: Theoretical Considerations and Available Evidence*, 324 J. AM. MED. ASS'N 441, 441 (2020).
[95] Julian W. Tang et al., *A Schlieren Optical Study of the Human Cough with and Without Wearing Masks for Aerosol Infection Control*, 6 J. ROYAL SOC'Y INTERFACE S727, S732 (2009).
[96] Siddhartha Verma et al., *Visualizing the Effectiveness of Face Masks in Obstructing Respiratory Jets*, 32 PHYSICS FLUIDS 061708-1, 061708-2 (2020).
[97] Sergey A. Grinshpun et al., *Performance of an N95 Filtering Facepiece Particulate Respirator and a Surgical Mask During Human Breathing: Two Pathways for Particle Penetration*, 6 J. OCCUPATIONAL & ENVTL. HYGIENE 593, 593 (2009).
[98] Patricia M. Holton et al., *Particle Size-Dependent Leakage and Losses of Aerosols in Respirators*, 48 AM. INDUS. HYGIENE ASS'N J. 848 (1987).
[99] Ignazio M. Viola et al., *Face Coverings, Aerosol Dispersion and Mitigation of Virus Transmission Risk*, 2 IEEE OPEN J. ENG'G MED. & BIOLOGY 26, 30 (2021).

masks simulated leakage and found that a hole equal to ~1% of the mask area decreased mask efficiency by over 60%.[103] Even in professional settings with high-grade, non-cloth masks, a poor fit can allow air to leak.[104,105,106] Double-masking reduces, but does not eliminate, such leakage.[107,108] In a study of N95 respirators, 25% (158 of 643) professional healthcare workers failed to properly fit their mask, despite knowing they were being studied and receiving instructions on how to achieve a proper respirator fit.[109] Unlike respirators, which protect their wearers from airborne particles, surgical masks are intended to protect those other than the wearer, and have a much looser fit. Cloth masks may be looser still, followed by homemade masks.[110,111]

Laboratory evidence supports the ability of masks to serve a source-control function. Multiple studies have demonstrated that masks can reduce the number of bacterial colonies that grow on petri dishes placed in front of subjects who are directed to cough with or without a

---

[100] Marianne Van der Sande et al., *Professional and Home-Made Face Masks Reduce Exposure to Respiratory Infections Among the General Population*, 3 PLOS ONE 1, 2 (2008).
[101] Anna Davies et al., *Testing the Efficacy of Homemade Masks: Would They Protect in an Influenza Pandemic?*, 7 DISASTER MED. & PUB. HEALTH PREPAREDNESS 413, 415 (2013).
[102] Eugenia O'Kelly et al., *Comparing the Fit of N95, KN95, Surgical, and Cloth Face Masks and Assessing the Accuracy of Fit Checking*, 16 PLOS ONE 1, 2 (2021).
[103] Abhiteja Konda et al., *Aerosol Filtration Efficiency of Common Fabrics Used in Respiratory Cloth Masks*, 14 ACS NANO 6339, 6345 (2020).
[104] Klaus Willeke et al., *New Methods for Quantitative Respirator Fit Testing with Aerosols*, 42 AM. INDUS. HYGIENE ASS'N 121, 121 (1981).
[105] *PortaCount Plus Respirator Fit Tester and N95-Companion*, TSI INC., https://www.tsi.com/getmedia/e39e2877-ef0d-43d3-8667-b8f941f94df55/PortaCount2980083RevE?ext=.pdf (last visited Nov. 11, 2020).
[106] Angela Weber et al., *Aerosol Penetration and Leakage Characteristics of Masks Used in the Health Care Industry*, 21 AM. J. INFECTION CONTROL 167, 172 (1993) (noting that better-performing respirators can increase breathing resistance, increasing the likelihood that particles could be pulled into the mask through face-seal leaks).
[107] Emily E. Sickbert-Bennett et al., *Fitted Filtration Efficiency of Double Masking During the COVID-19 Pandemic*, 181 JAMA INTERNAL MED. 1126, 1126 (2021
[108] Venugopal Arumuru et al., *Double Masking Protection vs. Comfort—A Quantitative Assessment*, 33 PHYSICS FLUIDS 077120 (2021).
[109] Quinn Danyluk et al., *Health Care Workers and Respiratory Protection: Is the User Seal Check a Surrogate for Respirator Fit-Testing?*, 8 J. OCCUPATIONAL & ENVTL. HYGIENE 267, 268 (2011).
[110] Marianne Van der Sande et al., *Professional and Home-Made Face Masks Reduce Exposure to Respiratory Infections Among the General Population*, 3 PLOS ONE 1, 3 (2008).
[111] Catherine M. Clase et al., *Forgotten Technology in the COVID-19 Pandemic: Filtration Properties of Cloth and Cloth Masks—A Narrative Review*, 95 MAYO CLINIC PROC. 2204, 2215 (2020).

mask,[112,113,114,115 116,117,118] and one study using reverse-transcription polymerase chain reaction to detect viral particles on such dishes found similar results.[119] In a study of surgical masks against influenza virus, viral RNA was detected in 78% (29 of 37 subjects) of exhaled human breath samples collected from subjects wearing masks, versus 95% (35 of 37 subjects) of those without masks.[120]

Most studies evaluating as-worn face mask efficacy use mannequin heads and compare the number of particles collected inside the mannequin's mask to outside it. Under these conditions, cloth masks have been shown to have highly variable filtration qualities. Cotton mask filtration efficiencies have been measured at between 15–40% when worn on mannequin heads, depending on the material used as an insert filter, when placed immediately next to an aerosol generator.[121] In an experiment in which 2 mannequins configured to simulate tidal breathing faced each other in a test chamber at greater distances of 25 cm to 100cm (<10 inches to 3.4 feet), placing a cloth mask on the source mannequin blocked more than 50% of virus transmission ($P<0.05$).[122] In one study in which cloth masks were placed on mannequins during

---

[112] Anna Davies et al., *Testing the Efficacy of Homemade Masks: Would They Protect in an Influenza Pandemic?*, 7 DISASTER MED. & PUB. HEALTH PREPAREDNESS 413 (2013).
[113] Brewster C. Doust & Arthur B. Lyon, *Face Masks in Infections of the Respiratory Tract*, 71 J. AM. MED. ASS'N 1216 (1918).
[114] C. G. Paine, *The Aetiology of Puerperal Infection*, 1 BRIT. MED. J. 243 (1935).
[115] R. A. Shooter et al., *A Study of Surgical Masks*, 47 BRIT. J. SURGERY 246 (1959).
[116] V. W. Greene & D. Vesley, *Method for Evaluating Effectiveness of Surgical Masks*, 83 J. BACTERIOLOGY 663 (1962).
[117] Louis B. Quesnel, *The Efficiency of Surgical Masks of Varying Design and Composition*, 62 BRIT. J. SURGERY 936 (1975).
[118] Charles F. McKhann et al., *Hospital Infections: A Survey of the Problem*, 55 AM. J. INFECTIOUS DISEASES CHILDREN 579 (1938).
[119] D. F. Johnson et al., *A Quantitative Assessment of the Efficacy of Surgical and N95 Masks to Filter Influenza Virus in Patients with Acute Influenza Infection*, 49 CLINICAL INFECTIOUS DISEASES 275 (2009).
[120] Donald K. Milton et al., *Influenza Virus Aerosols in Human Exhaled Breath: Particle Size, Culturability, and Effect of Surgical Masks*, 9 PLOS PATHOGEN 1, 2 (2013).
[121] W. C. Hill et al., *Testing of Commercial Masks and Respirators and Cotton Mask Insert Materials Using SARS-CoV-2 Virion-Sized Particulates: Comparison of Ideal Aerosol Filtration Efficiency Versus Fitted Filtration Efficiency*, 20 NANO LETTERS 7642, 7645 (2020).
[122] Hiroshi Ueki et al., *Effectiveness of Face Masks in Preventing Airborne Transmission of SARS-CoV-2*, 5 MSPHERE 1, 3 (2020).

simulated speaking or coughing, high-speed imaging showed that less than 0.1% of large droplets (>30 μm) escaped.[123] Another mannequin study found similar results, with masks blocking between 50–98% of 5 micron particles but only 0–55% of 0.5 micron particles when breathing outwards.[124] Cloth masks sewn to CDC specifications offered ~18% inward and 0% outward filtration efficacy at the 0.5 micron size, with inward/outward efficiencies improving as particle size increased.[125]

Surgical masks on mannequin heads tend to outperform cloth masks but still demonstrate variable results. One mannequin study found that between 5%–20% of respiratory secretions were captured by standard surgical masks during simulated tidal breathing due to face mask leakage, while better-fitting surgical masks ("SecureFit Ultra") captured ~50% of outward-moving particles.[126] Another study calculated the leakage of inward-moving particles from surgical masks and found that leakage rates were inversely related to particle size, decreasing from ~78% at 0.3 micron size to ~5% at the 10 micron size.[127] Other fitted filtration studies have reported similar findings.[128,129,130,131] Fewer mannequin studies have been conducting to evaluate the effects of surgical masks on actual viral particles. In one study, researchers aerosolized influenza virus in 0.5 seconds 70 cm in front of a mannequin, collected samples in one minute,

---

[123] Lucia Bandiera et al., *Face Coverings and Respiratory Tract Droplet Dispersion*, 7 ROYAL SOC'Y OPEN SCI. 1, 6 (2020).
[124] Jin Pan et al., *Inward and Outward Effectiveness of Cloth Masks, a Surgical Mask, and a Face Shield*, 55 AEROSOL SCI. & TECH. 718, 728 fig.7 (2021).
[125] *Id.*
[126] Rajeev B. Patel et al., *Respiratory Source Control Using a Surgical Mask: An In Vitro Study*, 13 J. OCCUPATIONAL & ENVTL. HYGIENE 569, 575 fig.6 (2016).
[127] Gholamhossein Bagheri et al., *Face-Masks Save Us from SARS-CoV-2 Transmission*, ARXIV 1 (2021), https://arxiv.org/pdf/2106.00375.
[128] Phillip Clapp et al., *Evaluation of Cloth Masks and Modified Procedure Masks as Personal Protective Equipment for the Public During the COVID-19 Pandemic*, 181 JAMA INTERNAL MED. 463, 463 (2021).
[129] William G. Lindsley et al., *Efficacy of Face Masks, Neck Gaiters and Face Shields for Reducing the Expulsion of Simulated Cough-Generated Aerosols*, 55 AEROSOL SCI. & TECH. 449, 449 (2021).
[130] Amy V. Mueller et al., *Quantitative Method for Comparative Assessment of Particle Removal Efficiency of Fabric Masks as Alternatives to Standard Surgical Masks for PPE*, 3 MATTER 950, 950 (2020).
[131] John T. Brooks et al., *Maximizing Fit for Cloth and Medical Procedure Masks to Improve Performance and Reduce SARS-CoV-2 Transmission and Exposure, 2021*, 70 MORBIDITY & MORTALITY WKLY. REP. 254, 254 (2021).

and compared the amount of recovered virus from inside and outside the mask.[132] Researchers reported an average 83% reduction in viral particles with a range of 9–98% against particles between 1–200 microns in size, though the study's applicability to long-term mask use in real-life situations is unclear and researchers did not test either cloth masks or surgical masks with ear loops.[133]

Two mechanistic source control studies evaluated the impact of surgical masks against actual SARS-CoV-2 particles. In one study, 7 COVID-19 positive patients were asked to cough five times onto a petri dish placed 20 cm in front of their mouths—researchers reported that, compared to coughing without a mask, surgical masks were associated with reduced viral load in three cases, increased viral load in two cases, and in two cases they did not detect virus in either sample.[134] In another, surgical masks eliminated detectable coronavirus particles in both respiratory droplets and aerosols after infected subjects breathed into an air collection device for 30 minutes, but most (60%) respiratory samples of unmasked individuals also failed to contain detectable virions.[135]

Nonetheless, even partial filtration could be beneficial by reducing viral concentration, which may reduce the chance of transmission and the severity of disease.[136] The infective dose

---

[132] C. Makison Booth et al., *Effectiveness of Surgical Masks Against Influenza Bioaerosols*, 84 J. HOSP. INFECTION 22, 24 (2013).
[133] *Id.* at 23.
[134] Min-Chul Kim et al., *Effectiveness of Surgical, KF94, and N95 Respirator Masks in Blocking SARS-CoV-2: A Controlled Comparison in 7 Patients*, 52 INFECTIOUS DISEASES 908, 910 (2020).
[135] Nancy H. Leung et al., *Respiratory Virus Shedding in Exhaled Breath and Efficacy of Face Masks*, 26 NATURE MED. 676, 679 tbl.1b (2020).
[136] Monica Gandhi et al., *Masks Do More Than Protect Others During COVID-19: Reducing the Inoculum of SARS-Cov-2 to Protect the Wearer*, 35 GEN. INTERNAL MED. 3063, 3063 (2020).

for SARS-CoV-2 is not known but some commentators have speculated a number of between 100 and 700 virions.[137]

III. Clinical and observational evidence in the COVID-19 setting

Laboratory evidence is suggestive, but only high-quality clinical evidence can definitively establish the impact of cloth mask wearing under real-world conditions. Unfortunately, only two randomized controlled trials (RCT) have evaluated the efficacy of cloth face masking against the spread of COVID-19.

One study of 4862 participants in Denmark ("DANMASK") who reported being outside the home for more than 3 hours per day found no statistically significant difference between a group receiving a recommendation to wear a surgical mask when outside the home and the control group (1.8% (n=42) of the masked intervention group became infected vs. 2.1% (n=53) of the control group).[138] The DANMASK study relied on self-reported adherence,[139] was not designed to test the efficacy of masks as source control,[140] and did not consider whether COVID-19 positive participants were infected in the home,[141] among other limitations.[142,143]

A second, high-quality, cluster-randomized study of more than 342,000 adults spread across 600 villages in rural Bangladesh found that placement in the study's intervention group

---

[137] Sedighe Karimzadeh et al., *Review of Infective Dose, Routes of Transmission, and Outcome of COVID-19 Caused by the SARS-CoV-2 Virus: Comparison with Other Respiratory Viruses*, 149 EPIDEMIOLOGY & INFECTION 1, 6 (2021).

[138] Henning Bundgaard et al., *Effectiveness of Adding a Mask Recommendation to Other Public Health Measures to Prevent SARS-CoV-2 Infection in Danish Mask Wearers: A Randomized Controlled Trial*, 174 ANNALS INTERNAL MED. 335, 335 (2021).

[139] Christine Laine et al., *The Role of Masks in Mitigating the SARS-CoV-2 Pandemic: Another Piece of the Puzzle*, 174 ANNALS INTERNAL MED. 419, 419 (2021).

[140] Vinay Prasad, *Here's How to Think About the Danish Mask Study*, MEDPAGE TODAY, Nov. 18, 2020, https://www.medpagetoday.com/blogs/vinay-prasad/89778 (last visited Sep. 5, 2021).

[141] *Comments on DANMASK-19 Study*, ANNALS INTERNAL MED., https://www.acpjournals.org/doi/10.7326/M20-6817 (last visited Sep. 5, 2021).

[142] Thomas R. Frieden & Shama Cash-Goldwasser, *Of Masks and Methods*, 174 ANNALS INTERNAL MED. 421, 421 (2021).

[143] Henning Bundgaard et al., *Face Masks for the Prevention of COVID-19-Rationale and Design of the Randomised Controlled Trial DANMASK-19*, 67 DANISH MED. J. 1 (2020).

increased mask-wearing by 28.8% (from 13.3 to 42.3%),[144] with participants in control villages (n=13,893) reporting a 1% higher rate of symptoms of COVID-like illness than participants in intervention villages (n=13,273) (8.6% v. 7.6%; P=0.000).[145] Similar relative rate differences were noted for the study's primary outcome, symptomatic seroprevalence (positive blood test plus COVID-19 symptoms), with control and intervention prevalence rates of 0.80% and 0.71%, respectively (P=0.043).[146] Researchers also reported results by mask type, finding that surgical masks reduced symptomatic seroprevalence rates by 0.09% compared to controls (0.67% vs. 0.76%, P=0.043), but that cloth masks did not offer a statistically significant rate reduction (cloth mask: 0.74%, control: 0.76%, P=0.540).[147] A secondary endpoint of symptoms without serologic confirmation favored face masking generally,[148] but this endpoint is highly bias susceptible and the difference in the cloth mask subgroup, although borderline statistically significant, was less than 1% (cloth mask group: 7.9% v. 8.6%, p=0.048). Communities assigned to masking may report symptoms differently, and the more rigorous endpoint of laboratory-confirmed prior SARS-CoV-2 infection found no benefit.

The Bangladesh cluster RCT is applicable to the unique circumstances of the region. Natural immunity at the outset of the study was very low due to low case numbers, vaccination was largely absent, and children and schools were not included. Unfortunately, this trial is limited in its ability to inform regions with higher rates of natural immunity, higher rates of

---

[144] Jason Abaluck et al., *The Impact of Community Masking on COVID-19: A Cluster-Randomized Trial in Bangladesh*, at 18, WORKING PAPER, Aug. 31, 2021, https://www.poverty-action.org/sites/default/files/publications/Mask_RCT____Symptomatic_Seropositivity_083121.pdf (last visited Sep. 4, 2021).
[145] *Id.* at 22.
[146] *Id.* at 23.
[147] *Id.*
[148] *Id.* at 24.

vaccination, or school policies. A large RCT (n= ~40,000) in Guinea-Bissau on community cloth face mask use against COVID-19 is ongoing.[149]

The remainder of the availabie clinical evidence is primarily limited to non-randomized observational data, which are subject to confounding. Several studies of so-called "natural experiments"[150] found suggestive results of mask effectiveness by comparing case rates in locations implementing mask mandates with those that did not. A widely-cited U.S. study by Lyu et al. of state-wide executive orders requiring masks during the early months of the COVID-19 pandemic found reductions in the average daily county-level growth rate of between 0.9 and 2.0 percentage points during each of a series of 5-day periods beginning 1 day after signing the mask order (days 1–5, 6–10, 11–15, 16–20, and 21+),[151] but declines began sooner than the mean 5.8-day incubation period would suggest could be plausibly connected to mask usage,[152] and researchers did not attempt to measure actual mask usage or the impact of mask mandates on mobility. The researchers' estimates that state mandates prevented up to 450,000 cases (and, assuming a 1% case fatality rate, 4,500 deaths) by May 22, 2020 were repeated in news media despite the researchers' statement that their estimates "should be viewed cautiously."[153] A widely-cited, non-peer-reviewed analysis from Goldman Sachs based in part on mask mandate

---

[149] *Locally Produced Cloth Face Mask and COVID-19 Like Illness Prevention*, U.S. NAT'L LIBRARY OF MED., https://clinicaltrials.gov/ct2/show/NCT04471766 (last visited Nov. 16, 2020).
[150] Mark Petticrew et al., *Natural Experiments: An Underused Tool for Public Health?*, 119 PUB. HEALTH 751 (2005).
[151] Wei Lyu & George L. Wehby, *Community Use of Face Masks and COVID-19: Evidence from a Natural Experiment of State Mandates in the US*, 39 HEALTH AFFAIRS 1419, 1422 (2020).
[152] Conor McAloon et al., *Incubation Period of COVID-19: A Rapid Systematic Review and Meta-Analysis of Observational Research*, 10 BMJ OPEN 1, 6 fig.3 (2020).
[153] Wei Lyu & George L. Wehby, *Community Use of Face Masks and COVID-19: Evidence from a Natural Experiment of State Mandates in the US*, 39 HEALTH AFFAIRS 1419, 1423 (2020).

data from the Lyu et al. study concluded a national mask mandate could reduce the daily growth rate in infections in states without a mandate from 2.9% to 1%.[154]

Another study of data from 24 counties (23%) in Kansas that abided by the governor's mask mandate (or adopted their own) and 81 counties (77%) that opted out of the mandate found a decline in incidence from 17 to 16 per 100,000 in the former and an increase from 6 to 12 per 100,000 in the latter.[155] However, the choice of opting in or out of the mask mandate suggests different attitudes toward COVID-19 that may have affected other behavioral choices, and six cities in non-mask mandated counties also had mask ordinances in place at the time.[156] In at least 13 (54%) of the 24 mandated counties, mask mandates occurred alongside other mandated or recommended county-level mitigation strategies (e.g., gathering size limitations).[157] Notably, both sets of counties experienced large increases in case rates in the month following the publication of this study.[158]

Other natural experiment studies have similarly taken advantage of differential timing of mask mandates or other interventions to determine the effects of mask wearing on COVID-19 infection rates, generally finding that mask mandates substantially reduced the growth rate of infections and deaths.[159,160,161,162,163,164,165,166,167] Although some of these studies attempt to

---

[154] J. Hatzius et al., *Face Masks and GDP*, GOLDMAN SACHS, June 29, 2020, https://www.goldmansachs.com/insights/pages/face-masks-and-gdp.html (last visited Sep. 5, 2021).
[155] Miriam E. Van Dyke et al., *Trends in County-Level COVID-19 Incidence in Counties With and Without a Mask Mandate—Kansas, June 1–August 23, 2020*, 69 MORBIDITY & MORTALITY WKLY. REP. 1777, 1779 tbl. (2020).
[156] *Id.* at 1779.
[157] *Id.* at 1778.
[158] @youyanggu, Twitter (Dec. 12, 2020), https://twitter.com/youyanggu/status/1339306972189843456. ("A CDC paper last month found that Kansas counties with mask mandates saw a decrease in cases in Aug, while counties without mandates saw an increase. Since then, both groups saw a huge surge. Counties w/mandates are doing a bit better, but it's difficult to determine causation.")
[159] Victor Chernozhukov et al., *Causal Impact of Masks, Policies, Behavior on Early Covid-19 Pandemic in the U.S*, 220 J. ECONOMETRICS 23, 23 (2021).
[160] Alexander Karaivanov et al., *Face Masks, Public Policies and Slowing the Spread of Covid-19: Evidence from Canada*, 78 J. HEALTH ECON. 1, 1 (2021).
[161] Timo Mitze et al., *Face Masks Considerably Reduce COVID-19 Cases in Germany: A Synthetic Control Method Approach*, 117 PROC. NAT'L ACAD. SCI. 32293, 32293 (2020).

control for behavioral changes by using, e.g., Google mobility data, those data may not capture key aspects of mobility changes, such as selective reductions in mobility by those individuals exhibiting symptoms (e.g., due to increased social stigma of coughing or knowledge that one will face a temperature screening), greater physical distancing within retail establishments or other locations,[168] or the availability of curbside or no-contact pickup. These studies also cannot easily control for non-mobility related measures that may correlate with mask mandates, such as reductions in verbal communication when masks are worn, increased use of sanitary wipes, installation of clear plastic barriers, customer capacity limitations, or adjustments to equipment settings that improve indoor ventilation or air filtration. In cases where mask mandates occurred alongside other public health interventions, such as school or business closure or shelter-in-place restrictions, disambiguating the effects of one component is challenging. Most studies readily admit to limitations such as these.

Country comparisons suffer from similar potential confounding. A multivariate analysis of 196 countries found that only four country-level characteristics correlated in a statistically significant manner with coronavirus mortality rates: duration since first COVID-19 case (coefficient: 0.1782, P<0.001), percentage of population over age 60 (coefficient: 0.0691, P<0.001), obesity prevalence (coefficient: 0.0196, P=0.02), and time since first mask

---

[162] M. S. Gallaway et al., *Trends in COVID-19 Incidence After Implementation of Mitigation Measures – Arizona, January 22-August 7, 2020*, 69 MORBIDITY & MORTALITY WKLY. REP. 1460, 1462 (2020).
[163] Vincent C. Cheng et al., *The Role of Community-wide Wearing of Face Mask for Control of Coronavirus Disease 2019 (COVID-19) Epidemic Due to SARS-CoV-2*, 81 J. INFECTION 107, 109–12 (2020).
[164] Xiaowen Wang et al., *Association Between Universal Masking in a Health Care System and SARS-CoV-2 Positivity Among Health Care Workers*, 324 J. AM. MED. ASS'N 703, 703 (2020).
[165] Heesoo Joo et al., *Decline in COVID-19 Hospitalization Growth Rates Associated with Statewide Mask Mandates — 10 States, March–October 2020*, 70 MORBIDITY & MORTALITY WKLY. REP. 212 (2021).
[166] Gery P. Guy et al., *Association of State-Issued Mask Mandates and Allowing On-Premises Restaurant Dining with County-Level COVID-19 Case and Death Growth Rates — United States, March 1–December 31, 2020*, 70 MORBIDITY & MORTALITY WKLY. REP. 350 (2021).
[167] Dhaval Adjodah et al., *Association Between COVID-19 Outcomes and Mask Mandates, Adherence, and Attitudes*, 16 PLOS ONE 1, 1 (2021).
[168] Gyula Seres et al., *Face Mask Use and Physical Distancing Before and After Mandatory Masking: Evidence from Public Waiting Lines*, (No. SP II 2020-305) WZB DISCUSSION PAPER 1, 1–2 (2020).

recommendation (coefficient: -0.1266, P<0.001).[169] However, the authors concede that "[s]urveys and observational data of mask-wearing by the public [were] unavailable for most countries" and that the simultaneous adoption of health policies can make it "difficult to tease out the relative importance of each."[170]

Another study compared the mask-wearing rate of people in multiple countries from March to April 2020 with coronavirus fatalities and concluded that the mask non-wearing rate in mid-March explained up to 72% of the variation in COVID-related deaths by mid-May.[171] The study's authors also noted that cultural differences may explain much of the differences in infection rates; in Japan, for example, most people do not talk on public transit which may reduce exhaled aerosols[172] and there is evidence to suggest that mask-wearing in Japan also correlates with other positive hygiene practices, such as hand washing and vaccination.[173]

Several observational studies have attempted to correlate mask-wearing with COVID-19 infection rates in contexts other than state- or country-wide government mask mandates, but suffer from similar potential confounding.[174] For example, studies examining the transmission of SARS-CoV-2 on airplanes have suggested lower rates of secondary cases on flights with masking compared to those without it,[175] but it is unclear whether differences in other factors such as passenger spacing, flight duration, passenger follow-up efforts, cough intensity of infected patients, or pre- or post-flight infection rates played a role. Flight conditions are also

---

[169] Christopher T. Leffler et al., *Association of Country-wide Coronavirus Mortality with Demographics, Testing, Lockdowns, and Public Wearing of Masks*, 103 AM. J. TROPICAL MED. & HYGIENE 2400, 2406 tbl.4 (2020).
[170] *Id.* at 2407.
[171] Daisuke Miyazawa & Gen Kaneko, *Face Mask Wearing Rate Predicts Country's COVID-19 Death Rates*, MEDRXIV 1, 16 (2020), https://www.medrxiv.org/content/10.1101/2020.06.22.20137745v4.full.pdf.
[172] *Id.* at 15.
[173] Koji Wada et al., *Wearing Face Masks in Public During the Influenza Season May Reflect Other Positive Hygiene Practices in Japan*, 12 BMC PUB. HEALTH 1, 3 (2012).
[174] Chris Kenyon, *Widespread Use of Face Masks in Public May Slow the Spread of SARS CoV-2: An Ecological Study*. MEDRXIV 1, 1 (2020), https://www.medrxiv.org/content/10.1101/2020.03.31.20048652v1.full.pdf.
[175] David O. Freedman & Annelies Wilder-Smith, *In-Flight Transmission of SARS-CoV-2: A Review of the Attack Rates and Available Data on the Efficacy of Face Masks*, 27 J. TRAVEL MED. 1, 6 (2020).

atypical in terms of passenger density, air filtration, the presence of pressurized cooling vents, and severely restricted mobility, limiting the ability to generalize any findings to the community context. Of 382 sailors on board the aircraft carrier USS Theodore Roosevelt who volunteered to complete a questionnaire (27% of the 1417 total sailors on board), those self-reporting "face covering" had a lower rate of SARS-CoV-2 infection than those who did not (55.8% vs. 80.8%), but other self-reported behaviors also correlated in a statistically significant manner with lower infection rates, including avoidance of common areas (53.8% vs. 67.5%) and increased distancing from others (54.7% vs. 70.0%).[176] A large U.S. cohort study (n=198,077) found similar results, with individuals who responded via Smartphone app to surveys as "always" wearing facemasks outside the home 62% less likely to report COVID-19 infection, although the study could not exclude the possibility that those "always" reporting mask wearing also engaged in other personal risk reduction measures.[177] Similar studies (one in the U.S. and two international) also found correlations between positive responses to mask survey questions and reduced infection rates, and had similar limitations.[178,179,180] A study in Hong Kong found 11 clusters of COVID-19 were related to mask-off settings (i.e. eating, karaoke, religious activities, etc.) while only 3 were related to mask-on (3 clusters) settings (i.e. workplace).[181] However, such mask-off activities may be inherently more risky than the mask-on workplace considered in the

---

[176] Daniel C. Payne et al., *SARS-CoV-2 Infections and Serologic Responses from a Sample of U.S. Navy Service Members – USS Theodore Roosevelt, April 2020*, 69 MORBIDITY & MORTALITY WKLY. REP. 714, 718 tbl. (2020).
[177] Sohee Kwon et al., *Association of Social Distancing and Face Mask Use with Risk of COVID-19*, 12 NATURE COMMC'NS 1, 7 (2021).
[178] Benjamin Rader et al., *Mask-Wearing and Control of SARS-CoV-2 Transmission in the USA: A Cross-Sectional Study*, 3 LANCET DIGITAL HEALTH. E148, E154 (2021).
[179] Gavin Leech et al., *Mass Mask-Wearing Notably Reduces COVID-19 Transmission*, MEDRXIV 1, 6 (2021), https://www.medrxiv.org/content/10.1101/2021.06.16.21258817v1.full.pdf.
[180] Ashwin Aravindakshan et al., *The Impact of Mask-Wearing in Mitigating the Spread of COVID-19 During the Early Phases of the Pandemic*, MEDRXIV 1, 1 (2021), https://www.medrxiv.org/content/10.1101/2020.09.11.20192971v2.full.pdf.
[181] Vincent C. Cheng et al., *The Role of Community-wide Wearing of Face Mask for Control of Coronavirus Disease 2019 (COVID-19) Epidemic Due to SARS-CoV-2*, 81 J. INFECTION 107, 109 (2020).

study, such as by involving larger numbers of people within a given unit of area, longer durations of contact, or greater face-to-face communication.

Without randomization, natural experiments and other observational evidence provide only weak evidence of effectiveness.[182] Even when they reveal meaningfully different infection rates, the groups being compared may not possess similar characteristics, preventing causal inference. For example, geographic comparisons do not account for the possibility that, in locations where legislators have sufficient political support to enact mask mandates, populations are likely to have different attitudes about COVID-19 that could affect behavior other than mask-wearing.[183] Four natural experiment studies measured mask usage rates, but each was based on self-reported surveys which are prone to bias and may not reflect actual behavior. One study, for example, found that while only 12% of individuals surveyed admitted to not wearing a mask, 90% were observed not wearing one, a finding the authors described as a "large and statistically significant discrepancy."[184] Lower case rates following mask mandates could be mediated by differential propensities to respond to new information with, for example, increased hand hygiene, voluntary business restrictions, physical distancing, or reduced time away from home or participation in certain activities. It is possible that mask mandates reduce infection rates by prompting media coverage or statements of public health officials that increase public awareness, or reducing the willingness of individuals to enter public spaces where masks are required rather than reducing transmission when they enter those spaces.[185,186]

---

[182] *Using Face Masks in the Community: First Update*, Feb. 15, 2021, EUR. CTR. FOR DISEASE PREVENTION & CONTROL, https://www.ecdc.europa.eu/en/publications-data/using-face-masks-community-reducing-covid-19-transmission (last visited Sept. 5, 2021).

[183] William F. Maloney & Temel Taskin, *Determinants of Social Distancing and Economic Activity During COVID-19: A Global View*, WORLD BANK POL'Y RESEARCH WORKING PAPER 1, 3 (2020).

[184] Aleksandra Jakubowski et al., *Self-reported vs Directly Observed Face Mask Use in Kenya*, 4 JAMA NETWORK OPEN 1, 3 (2021).

[185] Daniel J. McGrail et al., *Enacting National Social Distancing Policies Corresponds with Dramatic Reduction in COVID19 Infection Rates*, 15 PLOS ONE 1, 1 (2020).

Although some studies attempted to control for potentially confounding variables, it is unlikely that researchers were able to account for all of them or know which were most important, such as simultaneous public health interventions, the publication of new COVID-related research investigations, changes in the capacity to contact trace, the availability and use of more-rapid or less-expensive diagnostics, or attendance at large-scale public gatherings related to social causes, political rallies, or sporting events. Some studies used self-reporting to measure health behaviors (such as social distancing and mask wearing), but mask mandates could increase social pressure to report or overestimate adherence.

Several retrospective cohort studies have attempted to analyze behaviors among people who were either diagnosed with COVID-19 or had known SARS-CoV-2-positive contacts. One such study of 124 families found that family members reported wearing a mask "all the time" after illness onset more frequently in the 83 families without secondary cases than in the 41 families with such secondary cases (45.8% vs. 19.5%, P=.02).[187] However, members of families without secondary cases also more frequently ate separately after illness onset (65.1% vs. 39.0%, P=.008), more frequently self-isolated after illness onset (69.9% vs. 51.2%, P=.05), more frequently self-isolated within 2 days of illness onset (31.3% vs. 14.6%, P=.05), more frequently had more than 1 hour of ventilation (opening of windows) per day (76.5% vs. 57.5%, P=.02), and less frequently had incidents of "close contact" (within 1 meter) with the primary case (8.7% vs. 30.0%, P<0.001),[188] suggesting that many other behavioral factors could be relevant. A retrospective case-control study (n=1050) in Thailand found similar results and had similar

---

[186] Laura Matrajt & Tiffany Leung, *Evaluating the Effectiveness of Social Distancing Interventions to Delay or Flatten the Epidemic Curve of Coronavirus Disease*, 26 EMERGING INFECTIOUS DISEASES 1740, 1740 (2020).
[187] Yu Wang et al., *Reduction of Secondary Transmission of SARS-CoV-2 in Households by Face Mask Use, Disinfection and Social Distancing: A Cohort Study in Beijing, China*, 5 BMJ GLOBAL HEALTH 1, 5 tbl.1 (2020).
[188] *Id.*

limitations.[189] Interviews were conducted one to three months after index patient contact, possibly exacerbating recall bias and sample size selection issues.[190]

Several case reports support the use of masks. A report by the Centers for Disease Control and Prevention described 2 Missouri hair stylists who wore masks while symptomatic with COVID-19 and saw 139 clients, none of whom became ill.[191] However, exposure to the index patient was short (median: 15 minutes), clients faced away, and variables such as hand hygiene, extent of conversation, common surfaces available for touching, disinfection of those surfaces, shared locations where masks were doffed and donned, etc., were not evaluated. The report also suffered from diagnostic limitations: only 67 (48%) clients received PCR tests with the remainder reporting no symptoms, testing was offered on day 5 potentially leading to false negatives due to COVID-19's incubation period, and clients exposed during highest viral shedding time (2-3 days before symptoms appear; number of clients not reported) were not included. These limitations in the absence of prospective design, randomization, and control make causal inference challenging.

IV. Clinical evidence from illnesses other than COVID-19

In addition to the two RCTs in the COVID-19 setting, at least 14 RCTs have assessed the relationship between mask-wearing and other respiratory infections (**Table 1**). Five of these took place in communal living settings, eight in household settings, and one in a hospital.

Communal living RCTs

---

[189] Pawinee Doung-Ngern et al., *Case-Control Study of Use of Personal Protective Measures and Risk for SARS-CoV 2 Infection, Thailand*, 26 EMERGING INFECTIOUS DISEASES 2607, 2607 (2020).
[190] *Id.* at 2609.
[191] M. J. Hendrix et al., *Absence of Apparent Transmission of SARS-CoV-2 from Two Stylists After Exposure at a Hair Salon with a Universal Face Covering Policy – Springfield, Missouri, May 2020*, 69 MORBIDITY & MORTALITY WKLY. REP. 930, 930 (2020).

Four of the 5 RCTs examining the effectiveness of mask-wearing in communal settings failed to find statistically significant results. A 3-arm cluster-randomized study of rates of influenza-like illnesses (ILI) among 1178 students in University of Michigan residence halls failed to find a benefit from wearing face masks alone compared to an unmasked control group (11.7% (46/392) vs. 13.8% (51/370); adjusted cumulative rate ratio [RR]: 1.10),[192] but found that masks plus hand hygiene did provide benefit (8.9% (31/349) vs. 13.8% (51/370); RR: 0.78),[193] consistent with findings in an earlier similar cluster-randomized study by the same researchers.[194] A 3-arm study of 995 Hajj pilgrims randomized into health education (n=292, 29%), health education plus face mask (n=257, 26%), and control (n=446, 45%) groups reported adherence rates of 52% and 81% in its intervention arms, respectively, but found no association between face mask wearing compliance and the chance of developing an acute respiratory infection in 225 individuals within one week of returning (OR: 0.97).[195] In a pilot study of 164 Hajj pilgrims, 53% (28/53) no-mask contacts sleeping immediately adjacent to patients with known ILIs became symptomatic, while only 31% (11/36) of masked contacts did so (P=.04).[196] However, a much larger (n=7687) randomized controlled follow-up study by the same research group not only failed to show a statistically significant benefit for mask wearing, but the per-protocol analysis showed higher point estimates for mask wearers compared to non-mask wearers for both clinical respiratory infections (12% (97/828) vs. 9% (141/1497); odds ratio

---

[192] Allison E. Aiello et al., *Facemasks, Hand Hygiene, and Influenza Among Young Adults: A Randomized Intervention Trial*, 7 PLOS ONE 1, 6 tbls.3, S1, and S5 (2012).
[193] *Id.*
[194] Allison E. Aiello et al., *A Randomized Intervention Trial of Mask Use and Hand Hygiene to Reduce Seasonal Influenza-Like Illness and Influenza Infections Among Young Adults in a University Setting*, 14 INT'L J. INFECTIOUS DISEASES 491 (2010).
[195] Ebtihal Z. Abdin et al., *Effect of Use of Face Mask on Hajj-Related Respiratory Infection Among Hajjis from Riyadh: A Health Promotion Intervention Study*, 12 SAUDI EPIDEMIOLOGY BULL. 27, 27–28 (2005).
[196] Osamah Barasheed et al., *Pilot Randomised Controlled Trial to Testing Facemasks Effectiveness in Preventing Influenza-Like Illness Transmission Among Hajj Pilgrims*, 14 INFECTIOUS DISORDERS DRUG TARGETS 110, 113 tbl.1 (2014).

[OR]: 1.3) and laboratory-confirmed respiratory infections (50% (46/93) vs. 41% (50/122); OR: 1.2).[197] While a subsequent meta-analysis of 13 mostly cohort and cross-sectional studies looking at face mask use among Hajj pilgrims reported a statistically significant decrease in respiratory infections (RR: 0.89; P<.01), it cautioned that facemask effectiveness was still "inconclusive due to great heterogeneity in study [design]" and included only two RCTs in its analysis.[198]

Household RCTs

All of the eight RCTs examining the impact of face masks in household settings failed to find statistically significant results in intention-to-treat analyses, with one reporting a significant decrease in a sub-group, per-protocol analysis. Most of these studies recruited patients shortly after diagnosis with an ILI, randomized them into a treatment category, and then traced the number of household contacts who then become ill. The studies varied in whether or not the intervention group required mask-wearing for the index patient (source control), other household members, or both groups.

Two RCTs looked at the utility of facemasks as source-control measures to prevent secondary infection in household settings and neither study reported protective effects. One of these took place in France, and found that when index cases wore surgical face masks for the five days following diagnosis, there was no statistically significant difference in transmission compared to households in which index cases did not wear a mask (16.2% (24/148) vs. 15.8% (25/158)).[199] A nearly identical study in China that randomized 245 ILI index cases to mask (n=123) and no mask (n=122) groups—while only requiring mask-wearing until symptom

---

[197] Mohammad Alfelali et al., *Facemask Against Viral Respiratory Infections Among Hajj Pilgrims: A Challenging Cluster-Randomized Trial*, 15 PLOS ONE 1, 7 (2020).
[198] Osamah Barasheed et al., *Uptake and Effectiveness of Facemask Against Respiratory Infections at Mass Gatherings: A Systematic Review*, 47 INT'L J. INFECTIOUS DISEASES 105, 109 (2016).
[199] Laetitia Canini et al., *Surgical Mask to Prevent Influenza Transmission in Households: A Cluster Randomized Trial*, 5 PLOS ONE 1, 5 (2010).

abatement—found no statistically significant effects on intra-household rates of clinical respiratory illness (0.19% (4/2098) vs. 0.29% (6/2036)) or ILI (0.05% (1/2098) vs. 0.15% (3/2036)).[200]

One household RCT conducted in Australia attempted to determine the protective effect of masks for the wearer. The study, involving 245 adults in 145 families in which the index case was a child diagnosed with an ILI and in which parents were randomized to wear a surgical, P2 (an N95 equivalent), or no mask, showed no significant differences in secondary ILI infection rates at the individual level (surgical mask: 19/94 (20%); P2 mask: 14/92 (15%)) compared to the control group (16/100 (16%)).[201] A pre-planned per-protocol analysis found a statistically significant decrease (P=.015) in infection rates among adherent mask users (RR: 0.26),[202] but adherence was low (38% (36/94) of surgical and 46% (42/92) of P2 mask users reported wearing masks "most or all" of the time on the intervention's first day),[203] and adherent participants may have been more likely to engage in other protective behaviors.

Five RCTs evaluated the effects of mask wearing by all household members on secondary infection rates, with mixed results. A Thai study followed child influenza cases in 442 households with 1147 household members, randomized families into hand-washing (n= 292), hand-washing plus face masks (n=291), and control arms (n=302), and reported higher secondary ILI rates based on self-reported symptoms of 17% (50/292) in the hand-washing arm and 18% (51/291) in the hand-washing plus mask arm—compared to only 9% (26/302) in the control arm, and there were no significant differences in the primary outcome measure of

---

[200] Chandini R. MacIntyre et al., *Cluster Randomised Controlled Trial to Examine Medical Mask Use as Source Control for People with Respiratory Illness*, 6 BMJ OPEN 1, 5 tbl.2 (2016).
[201] Chandini R. MacIntyre et al., *Face Mask Use and Control of Respiratory Virus Transmission in Households*, 15 EMERGING INFECTIOUS DISEASES 233, 238 tbl.4 (2009).
[202] *Id.* at 237.
[203] *Id.* at 236.

influenza-like illness (OR: 0.5, P=.3).[209] A 19-month study of 617 New York City households that randomized families into three cohorts—hand sanitizer ("HS", n=205), HS plus face mask ("HS + mask", n=201), and an educational control group (n=211)—and followed them for 19 months while tracking respiratory infection rates found that the HS + mask group (OR: 0.82; 95% CI 0.70-0.97) outperformed the HS alone group (OR: 1.01; 95% CI 0.85-1.21), compared to the reference educational group.[210]

Healthcare settings

RCT evidence of face mask efficacy in healthcare settings is limited. One small RCT (n=32) of healthcare workers at a Japanese hospital found no statistically significant difference between mean number of days of cold symptoms reported by surgical face mask wearers (mean=16.1 days) and non-wearers (mean=14.3 days; P=.81) during the winter season.[211] And although surgical masks are ubiquitously worn during surgery because they are believed to prevent infection,[212,213,214] multiple studies have reported that the use of surgical masks as source control in operating theaters has not proven to reduce surgical site infection—with a Cochrane meta-analysis reporting mask v. no-mask infection rates of 1.8% (13/706) vs. 1.4% (10/723;

---

[209] Thorsten Suess et al., *The Role of Facemasks and Hand Hygiene in the Prevention of Influenza Transmission in Households: Results from a Cluster Randomised Trial; Berlin, Germany, 2009–2011*, 12 BMC INFECTIOUS DISEASES 1, 10 tbl.5 (2012).

[210] Elaine L. Larson et al., *Impact of Non-pharmaceutical Interventions on URIs and Influenza in Crowded, Urban Households*, 125 PUB. HEALTH REP. 178, 186 tbl.5 (2010).

[211] Joshua L. Jacobs et al., *Use of Surgical Face Masks to Reduce the Incidence of the Common Cold Among Health Care Workers in Japan: A Randomized Controlled Trial*, 37 AM. J. INFECTION CONTROL 417, 419 tbl.3 (2009).

[212] Neil W. Orr, *Is a Mask Necessary in the Operating Theatre?*, 63 ANNALS ROYAL COLL. SURGEONS ENG. 390 (1981).

[213] N. J. Mitchell & S. Hunt, *Surgical Face Masks in Modern Operating Rooms—A Costly and Unnecessary Ritual?*, 18 J. HOSP. INFECTION 239 (1991).

[214] M. G. Romney, *Surgical Face Masks in the Operating Theatre: Re-examining the Evidence*, 47 J. HOSP. INFECTION 251 (2001).

P>.05),[215] 0% (0/10) vs. 30% (3/10; P>.05),[216] and 10.5% (33/313) vs. 9.1% (31/340; P>.05)[217] from studies conducted in its literature review.[218]

Comparing types of masks

At least ten studies evaluate the clinical efficacy of different types of masks compared to one another, but without a no-mask control group most provide little insight into mask efficacy. Four RCTs, four meta-analyses, and one prospective cohort study found surgical masks were non-inferior to N95s for protection against respiratory infections,[219,220,221,222,223,224,225,226,227] and one found evidence that N95s provide greater protection than medical masks against self-

---

[215] Th G. Tunevall, *Postoperative Wound Infections and Surgical Face Masks: A Controlled Study*, 15 WORLD J. SURGERY 383 (1991).

[216] *See* also Geoffrey V. Chamberlain & Elizabeth Houang, *Trial of the Use of Masks in the Gynaecological Operating Theatre*, 66 ANNALS ROYAL COLL. SURGEONS ENG. 432 (1984) (finding an increased infection rate after major abdominal surgery when the surgical team did not wear masks (3 of 5 subjects) compared to when they did wear masks (0 of 4 subjects), but the finding was not statistically significant and the researchers also found higher bacterial counts in air samples taken during masked versus unmasked procedures (154 vs. 96 colony forming units)).

[217] Joan Webster et al., *Use of Face Masks by Non-scrubbed Operating Room Staff: A Randomized Controlled Trial*, 80 ANZ J. SURGERY 169 (2010).

[218] Marina Vincent & Peggy Edwards, *Disposable Surgical Face Masks for Preventing Surgical Wound Infection in Clean Surgery*, 4 COCHRANE DATABASE SYS. REV. 1, 8 (2016).

[219] Mark Loeb et al., *Surgical Mask vs N95 Respirator for Preventing Influenza Among Health Care Workers: A Randomized Trial*, 302 J. AM. MED. ASS'N 1865, 1870 (2009).

[220] Chandini R. MacIntyre et al., *A Randomized Clinical Trial of Three Options for N95 Respirators and Medical Masks in Health Workers*, 187 AM. J. RESPIRATORY & CRITICAL CARE MED. 960, 963 (2013) (finding that surgical mask use was not inferior to targeted N95 use).

[221] Lewis J. Radonovich et al., *N95 Respirators vs Medical Masks for Preventing Influenza Among Health Care Personnel: A Randomized Clinical Trial*, 322 J. AM. MED. ASS'N 824, 830 (2019).

[222] Youlin Long et al., *Effectiveness of N95 Respirators Versus Surgical Masks Against Influenza: A Systematic Review and Meta-Analysis*, 13 J. EVIDENCE-BASED MED. 93, 98 (2020).

[223] Jessica J. Bartoszko et al., *Medical Masks vs N95 Respirators for Preventing COVID-19 in Healthcare Workers: A Systematic Review and Meta-Analysis of Randomized Trials*, 14 INFLUENZA & OTHER RESPIRATORY VIRUSES 365 368 (2020).

[224] Tom Jefferson et al., *Physical Interventions to Interrupt or Reduce the Spread of Respiratory Viruses (Review)*, 11 COCHRANE DATABASE SYS. REV. 1, 6–7 (2020).

[225] Jeffrey D. Smith et al., *Effectiveness of N95 Respirators Versus Surgical Masks in Protecting Health Care Workers from Acute Respiratory Infection: A Systematic Review and Meta-Analysis*, 188 CAN. MED. ASS'N J. 567, 572 (2016).

[226] Sabine Haller et al., *Use of Respirator vs. Surgical Masks in Healthcare Personnel and Its Impact on SARS-CoV-2 Acquisition – A Prospective Multicentre Cohort Study*, MEDRXIV 1 (2021), https://www.medrxiv.org/content/10.1101/2021.05.30.21258080v1.full.pdf.

[227] Katarzyna Barycka et al., *Comparative Effectiveness of N95 Respirators and Surgical/Face Masks in Preventing Airborne Infections in the Era of SARS-CoV2 Pandemic: A Meta-Analysis of Randomized Trials*, 15 PLOS ONE 1 (2020).

reported clinical respiratory illness but not ILI.[228] However, a recent review found that evidence that N95s protect healthcare workers from clinical respiratory infections at all is "low-quality."[229] One meta-analysis of particular note, an April 2020 preprint of a Cochrane review of clinical evidence for both surgical and N95 masks, "did not find any differences in the clinical effectiveness of either type of mask in the setting of respiratory viral infection transmission to healthcare workers,"[230] although the review's final November version omitted this language.[231]

One RCT compared continually worn cloth masks with surgical masks in the healthcare setting, finding cloth masks were associated with ILI infection rates 13-times higher (13/569 or 2.28% for cloth masks; 1/580 or 0.17% for surgical masks) than surgical masks (RR=13.00).[232] The study has been criticized because it provided new surgical masks more frequently than cloth masks and lacked washing protocols for cloth masks,[233,234] but may provide insight into the effectiveness of community masking where washing protocols are similarly absent and reuse is frequent. A post-hoc, sub-group analysis of this data concluded that the difference in infection rates were largely explained by washing protocols—participants who hand-washed their cloth masks (77%) as opposed to using the hospital laundry (13%) reported infection rates more than

---

[228] Vittoria Offeddu et al., *Effectiveness of Masks and Respirators Against Respiratory Infections in Healthcare Workers: A Systematic Review and Meta-Analysis*, 65 CLINICAL INFECTIOUS DISEASES 1934, 1938 (2017).
[229] Primiano Iannone et al., *The Need of Health Policy Perspective to Protect Healthcare Workers During COVID-19 Pandemic. A GRADE Rapid Review on the N95 Respirators Effectiveness*, 15 PLOS ONE 1, 1 (2020).
[230] Tom Jefferson et al., *Physical Interventions to Interrupt or Reduce the Spread of Respiratory Viruses. Part 1 – Face Masks, Eye Protection and Person Distancing: Systematic Review and Meta-Analysis*, MEDRXIV 1, 12 (2020), https://www.medrxiv.org/content/10.1101/2020.03.30.20047217v2.full.
[231] Tom Jefferson et al., *Physical Interventions to Interrupt or Reduce the Spread of Respiratory Viruses (Review)*, 11 COCHRANE DATABASE SYS. REV. 1 (2020).
[232] Chandini R. MacIntyre et al., *A Cluster Randomised Trial of Cloth Masks Compared with Medical Masks in Healthcare Workers*, 5 BMJ OPEN 1, 6 tbl.2 (2015).
[233] Jeremy Howard et al., *Face Masks Against COVID-19: An Evidence Review*, 118 PROCEEDINGS NAT'L ACAD. SCI. 1, 7 (2021).
[234] Chandini R. MacIntyre & S. J. Hasanain, *Community Universal Face Mask Use During the COVID 19 Pandemic—From Households to Travellers and Public Spaces*, 27 J. TRAVEL MED. 1, 2 (2020).

twice as high (OR: 2.04) as the hospital laundry group.[235] A mask-comparison study of 1441 Chinese healthcare workers failed to find a statistically significant benefit to either N95 (Clinical Respiratory Illness [CRI]: 3.9%, P=.085; Influenza-like Illness [ILI]: 0.3%, P=.068; Lab-confirmed virus [LCV]: 1.4%, P=.02; Influenza [flu]: 0.3%, P=.051) or surgical face masks (CRI: 6.7%, P=.52; ILI: 0.6%, P=.33; LCV: 2.6%, P=.67; Flu: 1.0%, P=.73), compared to a convenience no-mask group (CRI: ~8.7%; ILI: ~1.7%; LCV: ~3.1%; Flu: ~1.3%) using four different disease outcomes (except for greater protections from N95s as compared to no masks with lab-confirmed viruses), but all point estimates favored mask-wearing.[236] The no-mask comparison group was a non-randomized convenience group composed of individuals from nine different hospitals, limiting the ability to draw reliable conclusions.

Observational studies of SARS-CoV-1 and pandemic influenza

Fourteen non-randomized observational studies conducted during the 2003 SARS-CoV-1 ("SARS") and 2009 H1N1 epidemics provide mixed correlational evidence for the efficacy of face masks against the spread of viral infections, but suffer from various types of potential bias and other limitations. Three SARS case-control studies and one H1N1 cross-sectional survey were undertaken outside the healthcare setting. One case-control study of patients in Beijing found that just 27% (26/94) of probable cases "always" wore a mask when going outside, compared to 43% (121/281) of uninfected controls (RR 0.3),[237] but controls were identified by sequential digit dialing to achieve "neighborhood matching," a method that may be likely to identify individuals who leave the home less frequently. Similarly, a case-control study of

[235] Chandini R. MacIntyre et al., *Contamination and Washing of Cloth Masks and Risk of Infection Among Hospital Health Workers in Vietnam: A Post Hoc Analysis of a Randomised Controlled Trial*, 10 BMJ OPEN 1, 4 (2020).
[236] Chandini R. MacIntyre et al., *A Cluster Randomized Clinical Trial Comparing Fit-Tested and Non-Fit-Tested N95 Respirators to Medical Masks to Prevent Respiratory Virus Infection in Health Care Workers: RCT of Face Masks in Health Workers*, 5 INFLUENZA & OTHER RESPIRATORY VIRUSES 170, 176 tbl.3 (2011).
[237] Jiang Wu et al., *Risk Factors for SARS Among Persons Without Known Contact with SARS Patients, Beijing, China*, 10 EMERGING INFECTIOUS DISEASES 210, 213 tbl.1 (2004).

probable SARS-positive patients in Hong Kong found that cases wore masks less frequently than controls (27.9% (92/330) vs. 58.7% (387/660)), but identified controls through random digit dialing. In addition, cases in the Hong Kong study were less likely than controls to report disinfecting living quarters thoroughly (46.6% (154/330) vs. 74.5% (492/660)) and washing hands >11 times a day (18.4% (61/330) vs. 33.7% (223/660)), suggesting possible confounding.[238] A survey of 7,448 Korean school-aged children during the H1N1 pandemic found that, of 466 respondents reporting "continuous" mask use, only 3% (14) were diagnosed with H1N1, compared to 5.8% (164/2819) of irregular users and 5.7% (239/4164) of non-users (P=.04), but the authors cautioned that the cross-sectional design precluded confirmation of a causal relationship.[239] A study in Vietnam (n=65) during the SARS-CoV-1 outbreak found that 7 of 154 (or 1 in 22) unmasked people who had known contact with a SARS-positive index case contracted SARS, compared to none (of 9) people who reported wearing a mask,[240] but a 1 in 22 chance yields a 72% probability that, of a sample of 7 non-mask-wearing individuals, none would contract the disease.

Due primarily to ease of recruitment and outbreak patterns, the 10 remaining studies recruited SARS and H1N1-positive workers in healthcare settings. Six case-control studies were conducted during the SARS-CoV-1 epidemic. A study of 758 healthcare workers caring for patients with SARS at a hospital in Guangzhou, China found that those reporting that they wore 2 multi-layer cotton masks were diagnosed with SARS 10.9% (59/541) of the time compared to

---

[238] Joseph T. Lau et al., *SARS Transmission, Risk Factors, and Prevention in Hong Kong*, 10 EMERGING INFECTIOUS DISEASES 587, 590 tbl.2 (2004).
[239] Choon O. Kim et al., *Is Abdominal Obesity Associated with the 2009 Influenza a (H1N1) Pandemic in Korean School-Aged Children?*, 6 INFLUENZA & OTHER RESPIRATORY VIRUSES 313, 315 tbl.1 (2012).
[240] P. A. Tuan et al., *SARS Transmission in Vietnam Outside of the Health-Care Setting*, 135 EPIDEMIOLOGY & INFECTION 392, 397 tbl.2 (2007).

27.6% (32/116) for those reporting wearing 1 multi-layer mask (P<0.001),[241] but there was no unmasked comparison group and the researchers concluded that they "did not find that wearing double layers of . . . multilayered cotton masks . . . [was] associated with being protected from SARS."[242] A univariate analysis of 477 Beijing hospital workers found that 5.5% (15/274) of those reporting that they wore 16-layer cotton surgical masks also had SARS compared to 17.7% (36/203) for those not reporting wearing this type of mask (P<0.001), but the same study failed to show efficacy for 12-layer cotton surgical masks (6.5% (8/123) vs. 12.1% (43/354), P=.07), N95 masks (6.1% (2/33) vs. 11.0% (49/444), P=.37), or disposable masks (11.6% (11/95) vs. 10.5% (40/382)).[243] A case-control study of 29 SARS-positive cases and 98 non-SARS controls at a hospital in Hanoi, Vietnam reported that cases wore masks less frequently than controls (32% (8/25) vs. 38.9% (35/90); P=.01),[244] but the authors cautioned that recall bias is particularly relevant where an exposure (mask usage) has a strong intuitive causal link with outcome, also noting that the results were likely less accurate than would be obtained in a blinded or matched case-control study.[245] A case-control study of 13 SARS-infected and 241 non-infected staff members at various Hong Kong hospitals found that cases wore masks much less often than controls (15% (2/13) vs. 70% (169/241); P=.0001).[246] In a study of 320 subjects hospitals in Hanoi, Vietnam, a multivariate logistic regression analysis of 85 (27%) of those subjects found a 12.6-fold protective effect associated with continuous mask-wearing compared to no mask wearing (aOR: 12.6, P<.01), but it is unclear how the 85 subjects were selected and whether the

---

[241] Wei-Qing Chen et al., *Which Preventive Measures Might Protect Health Care Workers from SARS?*, 9 BMC PUB. HEALTH 1, 5 tbl.3 (2009).
[242] *Id.* at 7.
[243] Wei Liu et al., *Risk Factors for SARS Infection Among Hospital Healthcare Workers in Beijing: A Case Control Study*, 14 TROPICAL MED. & INT'L HEALTH 52, 55 tbl.2 (2009) (raw numbers back-calculated from Table 2 data).
[244] Hiroshi Nishiura et al., *Rapid Awareness and Transmission of Severe Acute Respiratory Syndrome in Hanoi French Hospital, Vietnam*, 73 AM. J. TROPICAL MED. & HYGIENE 17, 20 tbl.2 (2005).
[245] *Id.* at 22.
[246] W. H. Seto et al., *Effectiveness of Precautions Against Droplets and Contact in Prevention of Nosocomial Transmission of Severe Acute Respiratory Syndrome (SARS)*, 361 LANCET 1519, 1520 tbl.2 (2003).

selection process created a risk of bias, and interviews were conducted 7 or more months after the beginning of the SARS epidemic, creating a risk of reporting bias.[247]

Four observational studies of healthcare workers were conducted during the H1N1 influenza pandemic. A case-control study at a hospital in Hong Kong found that in the 4 cases neither the index patients nor the exposed persons wore a mask (or could not recall whether they wore a mask), while among controls approximately two-thirds of index patients wore masks (0% (0/4) vs. 63.9% (532/832), P=.01).[248] Similarly, a case-control study at a hospital in Kobe, Japan found that 96% (79/82) of controls "always" wore masks but only 80% (4/5) of cases, a difference that was not statistically significant.[249] A case-control study of healthcare workers in Beijing during the H1N1 pandemic did not show a benefit associated with continuous mask-wearing: 71.6% (146/204) of controls wore masks most of their working time vs. 72.5% (37/51) of cases.[250]

A Cochrane meta-analysis of 7 of the above case-control studies conducted during the SARS-CoV-1 epidemic found that 39.4% (268/681) of cases reported mask wearing compared to 62.0% (1573/2535) of controls.[251] The authors concluded that "simple mask-wearing was highly effective (OR 0.32)," but also cautioned that 6 of the 7 studies had a medium or high risk of bias, and these 6 studies provided over 96% of the total number of cases and controls in the meta-analysis.[252] A more recent meta-analysis of 8 studies from the H1N1 influenza pandemic

---

[247] Ayako Nishiyama et al., *Risk Factors for SARS Infection Within Hospitals in Hanoi, Vietnam*, 61 JAPANESE J. INFECTIOUS DISEASE 388, 389 tbl.2 (2008).
[248] Vincent C. Cheng et al., *Prevention of Nosocomial Transmission of Swine-Origin Pandemic Influenza Virus A/H1N1 by Infection Control Bundle*, 74 J. HOSP. INFECTION 271 (2010).
[249] Takao Toyokawa et al., *Seroprevalence of Antibodies to Pandemic (H1N1) 2009 Influenza Virus Among Health Care Workers in Two General Hospitals After First Outbreak in Kobe, Japan*, 63 J. INFECTION 281, 286 tbl.5 (2011).
[250] Yi Zhang et al., *Associated with the Transmission of Pandemic (H1N1) 2009 Among Hospital Healthcare Workers in Beijing, China*, 7 INFLUENZA & OTHER RESPIRATORY VIRUSES 466, 469 tbl.2 (2013).
[251] Tom Jefferson et al., *Interventions for the Interruption or Reduction of the Spread of Respiratory Viruses*, 7 COCHRANE DATABASE SYS. REV. 1, 108 (2011) (Analysis 1.3).
[252] *Id.* at 11.

concluded that, overall, "facemask use was not significantly protective," and also cautioned that most studies included in the analysis had a moderate to high risk of bias.[253] Specific biases mentioned in these meta-analyses included, among others, selection bias, reporting bias, publication bias, and ascertainment bias, as well as concerns over non-specific definitions of what constituted "exposure," potential confounding of unmeasured protective (or harmful) behaviors, and lack of an adequate description of controls. Additionally, the infection dynamics of SARS-COV-1 and pandemic influenza differ from SARS-CoV-2, limiting the extent of insight these studies can provide. Ten of the 14 available studies evaluated exposures only in high-risk healthcare settings, which may differ from community interactions in duration, proximity, and frequency. Considered in view of available RCT evidence, such weaknesses place observational mask data in a skeptical light.

V. Meta-analyses

We identified 32 systematic reviews and meta-analyses evaluating the effects of community face masking against respiratory viral transmission. Of 16 quantitative meta-analyses (**Table 2**), 8 were critical or equivocal as to whether existing evidence was sufficient to support a public recommendation of masks, and the remaining 8 supported a public mask intervention on the basis of existing evidence primarily due to the precautionary principle—i.e., based on the assumption that masks might help and are unlikely to harm—and on the basis of observational or other indirect evidence. Of the 15 solely qualitative reviews identified by the authors, seven concluded that evidence for the use of community masking was weak,[254,255,256,257,258,259,260] seven

[253] Patrick Saunders-Hastings et al., *Effectiveness of Personal Protective Measures in Reducing Pandemic Influenza Transmission: A Systematic Review and Meta-Analysis*, 20 EPIDEMICS 1, 6 (2017).
[254] Roger Chou et al., *Masks for Prevention of Respiratory Virus Infections, Including SARS-CoV-2, in Health Care and Community Settings: A Living Rapid Review*, 173 ANNALS INTERNAL MED. 542, 553 (2020) ("[T]he evidence on mask use and risk for SARS-CoV-2 infection is very sparse.").
[255] Monica Taminato et al., *Homemade Cloth Face Masks as a Barrier Against Respiratory Droplets–Systematic Review*, 33 ACTA PAULISTA ENFERMAGEM 1, 8 (2020) ("[A]ny face mask, regardless of filtering efficiency . . . will

cautiously concluded that mask benefits outweigh risks in various settings, often conceding that the evidence was only of low to moderate quality,[261,262,263,264,265,266,267] and one unequivocally concluded that facemasks were beneficial.[268] Despite their varying conclusions, these 15

---

have a marginal impact if not used in connection to other measures, such as . . . social distancing . . . and regular hand hygiene.").

[256] Samir Benkouiten et al., *Non-pharmaceutical Interventions for the Prevention of Respiratory Tract Infections During Hajj Pilgrimage*, 12 TRAVEL MED. & INFECTIOUS DISEASE 429, 437 (2014) (characterizing the results of face mask studies in preventing respiratory illnesses as "contradictory").

[257] Ali Mostafaei et al., *Can Wearing a Face Mask Protect from COVID-19? A Systematic Review*, 14 IRANIAN J. MED. MICROBIOLOGY 101, 104 (2020) (describing the level of evidence that facemasks alone provide protection against respiratory infection as "low to moderate").

[258] Faisal bin-Reza et al., *The Use of Masks and Respirators to Prevent Transmission of Influenza: A Systematic Review of the Scientific Evidence*, 6 INFLUENZA & OTHER RESPIRATORY VIRUSES 257, 265 (2012) ("[T]here is a limited evidence base to support the use of masks and/or respirators in healthcare or community settings.").

[259] Benjamin J. Cowling et al., *Face Masks to Prevent Transmission of Influenza Virus: A Systematic Review*, 138 EPIDEMIOLOGY & INFECTION 449, 455 (2010) ("There is little evidence to support the effectiveness of face masks to reduce the risk of infection.").

[260] Amir Qaseem et al., *Use of N95, Surgical, and Cloth Masks to Prevent COVID-19 in Health Care and Community Settings: Living Practice Points From the American College of Physicians (Version 1)*, 173 ANNALS INTERNAL MED. 642, 646 tbl.4 (2020) ("The evidence is very uncertain about the effectiveness of cloth masks . . . compared with no masks on the risk for SARS-CoV-1 infection."); *see also id.* at 647 ("The CDC does not consider cloth masks as PPE [personal protective equipment] in health care settings, given the lack of evidence of their effectiveness against transmission of SARS-CoV-2.").

[261] Jeremy Howard et al., *Face Masks Against COVID-19: An Evidence Review*, 118 PROCEEDINGS NAT'L ACAD. SCI. 1, 6 (2021) ("The positive impact of public mask wearing . . . is 'scientifically plausible but uncertain'.").

[262] Mehr Jain et al., *Efficacy and Use of Cloth Masks: A Scoping Review*, 12 CUREUS 1, 10 (2020) ("Cloth masks are shown to have limited inward protection in healthcare settings where viral exposure is high but may be beneficial for outward protection in low-risk settings and use by the general public where no other alternatives to medical masks are available.").

[263] Milena Santos et al., *Are Cloth Masks a Substitute to Medical Masks in Reducing Transmission and Contamination? A Systematic Review*, 34 BRAZILIAN ORAL RESEARCH 1, 15 (2020) ("Cloth masks seem to provide some degree of protection" but "the quality of evidence about efficiency is very low to moderate.").

[264] Chandini R. MacIntyre & Abrar A. Chughtai, *A Rapid Systematic Review of the Efficacy of Face Masks and Respirators Against Coronaviruses and Other Respiratory Transmissible Viruses for the Community, Healthcare Workers and Sick Patients*, 104 INT'L J. NURSING STUDIES 1, 5 (2020) (Use of masks as source control is "a sensible recommendation given the suggestion of protection.").

[265] Mary Abboah-Offei et al., *A Rapid Review of the Use of Face Mask in Preventing the Spread of COVID-19*, 3 INT'L J. NURSING STUDIES ADVANCES 1, 26 (2020) ("[T]he efficacy of some face mask types . . . such as . . . cloth has not been established . . . .").

[266] P. B. Smith et al., *A Scoping Review of Surgical Masks and N95 Filtering Facepiece Respirators: Learning from the Past to Guide the Future of Dentistry*, 131 SAFETY SCI. 1, 6 (2020) ("Current sterilization measures are not sufficient to permit routine reuse of facemasks.").

[267] Maria C. de Camargo et al., *Effectiveness of the Use of Non-woven Face Mask to Prevent Coronavirus Infections in the General Population: A Rapid Systematic Review*, 25 CIENCIA & SAUDE COLETIVA 3365, 3374 (2020) ("The results regarding masks effectiveness were conflicting.").

[268] Madhu Gupta et al., *The Use of Facemasks by the General Population To Prevent Transmission of COVID 19 Infection: A Systematic Review*, MEDRXIV 1 (2020), https://www.medrxiv.org/content/10.1101/2020.05.01.20087064v1.full.pdf.

qualitative reviews are largely redundant of one another and chiefly evaluate evidence already discussed above.

The meta-analyses largely analyzed the same RCTs as one another but used different methodologies and sometimes included different non-RCT observational studies. None of these studies considered the SARS-CoV-2 virus specifically, and most looked at surgical—not cloth—face mask use in community settings.

VI. Evidence suggestive of face mask harm

Although high-quality evidence may eventually support recommendations to wear masks that are currently based on the precautionary principle or optimistic interpretations of observational data that have potentially important limitations, it is important to consider the an alternate possibility: that community masking may accelerate rather than reduce transmission of infectious disease. Although some evidence suggests masks may cause non-infection-related harms, such as breathing difficulties,[269,270] psychological burdens,[271] impaired communication,[272,273] skin irritation or breakdown,[274,275] and headaches,[276] the most concerning potential harm to health is an increased rate of disease spread.

---

[269] Jian H. Zhu et al., *Effects of Long-Duration Wearing of N95 Respirator and Surgical Facemask: A Pilot Study*, 4 J. LUNG PULMONARY & RESPIRATORY RESEARCH 97, 97 (2014) (discussing nasal resistance as a result of physiology changes due to N95s).

[270] Mina Bakhit et al., *Downsides of Face Masks and Possible Mitigation Strategies: A Systematic Review and Meta-Analysis*, 11 BMJ OPEN 1, 9 tbl.2 (2021).

[271] Jennifer L. Scheid et al., *Commentary: Physiological and Psychological Impact of Face Mask Usage during the COVID-19 Pandemic*, 17 INT'L J. ENVTL. RESEARCH & PUB. HEALTH 6655 (2020).

[272] Divya Swaminathan & Shoba S. Meera, *Masks Mask Communication – Communicating with Children in Health Care Settings*, 88 INDIAN J. PEDIATRICS 283 (March 2021).

[273] Katharina Hufner et al., *On the Difficulties of Building Therapeutic Relationships when Wearing Face Masks*, 138 J. PSYCHOSOMATIC RESEARCH 110226 (2020).

[274] Elisheva Rosner, *Adverse Effects of Prolonged Mask Use Among Healthcare Professionals During COVID-19*, 6 J. INFECTIOUS DISEASE EPIDEMIOLOGY 1 (2020).

[275] Jeff Donovan & Sandy Skotnicki-Grant, *Allergic Contact Dermatitis from Formaldehyde Textile Resins in Surgical Uniforms and Nonwoven Textile Masks*, 18 DERMATITIS 40, 40 (2007).

[276] Jonathan J. Ong et al., *Headaches Associated with Personal Protective Equipment—A Cross-Sectional Study Among Frontline Healthcare Workers During COVID-19*, 60 HEADACHE: THE J. HEAD & FACE PAIN 864, 864 (2020) (finding that most healthcare workers in the study develop "de novo PPE-associated headaches" as a result of wearing PPE including facemasks).

A number of studies have found higher point estimates of infection among mask wearers, some of which were statistically significant (**Table 3**). A study of healthcare workers returning from the Hajj reported that intermittent use of face masks was associated with a higher rate of acute respiratory tract infections than not wearing masks (34% (42/122) vs. 22% (4/18)), but also found that using masks "all the time" was associated with a lower infection rate (16% (18/110)).[277] Another Hajj study reported that "[u]nvaccinated pilgrims in the Facemask group had a higher rate of CRI than their counterpart in the Control group (13% versus 10%, P=0·03)."[278]

Multiple household studies have found higher instances of respiratory sickness in masked intervention groups than in unmasked controls. In one household source-control medical mask trial, point estimates of the primary outcome measure of ILI in the intention-to-treat analysis were higher in the surgical mask group than in the no mask group (22.3% (21/94) vs. 16.0% (16/100)), but the results were not statistically significant and adherence was poor.[279] In a study of 509 households comprised of 2,788 individual members, households in the hand sanitizer group included significantly more members without any reported upper respiratory symptoms compared to the hand sanitizer plus face mask group (57.6% (545/946) vs. 38.7% (363/938), P<0.01).[280] In the Thai study discussed previously, there were higher point estimates of the primary outcome measure of laboratory-confirmed secondary infections among members in the hand washing plus mask group compared to the control group (23% (66/291) vs. 19% (58/302), n.s.), higher rates of such infections at the household level (35% vs. 22%), and in an analytic

[277] Saeed Al-Asmary et al., *Acute Respiratory Tract Infections Among Hajj Medical Mission Personnel, Saudi Arabia*, 11 INT'L J. INFECTIOUS DISEASE 268, 270 tbl.2 (2007).
[278] Mohammad Alfelali et al., *Facemask Against Viral Respiratory Infections Among Hajj Pilgrims: A Challenging Cluster-Randomized Trial*, 15 PLOS ONE 1, 8 (2020).
[279] Chandini R. MacIntyre et al., *Face Mask Use and Control of Respiratory Virus Transmission in Households*, 15 EMERGING INFECTIOUS DISEASES 233, 238 tbl.4 (2009).
[280] Elaine L. Larson et al., *Impact of Non-pharmaceutical Interventions on URIs and Influenza in Crowded, Urban Households*, 125 PUB. HEALTH REP. 178, 184 tbl.2 (2010).

subset of 348 households with 885 members (with 94 co-index households removed), a statistically significant increase in ILI for those in the mask group (OR: 2.15, P=0.004) that the researchers described as "twofold in the opposite direction from the hypothesized protective effect."[281]

In a cluster-randomized trial of cloth masks compared with medical masks in healthcare workers, rates of ILI in the cloth mask intervention arm, where 56.8% of workers wore a mask more than 70% of the time, were more than 3 times higher compared to the "standard practice" control arm, where 23.6% did so (2.3% (13/569) vs. 0.7% (3/458)).[282] Researchers noted that because the Institutional Review Board deemed it unethical to ask participants not to use a mask (presumably because of beliefs about the effectiveness of masks in preventing infection), they were unable to include a no-mask control group.[283]

VII. Discussion

Taken as a whole, the available mechanistic and clinical evidence leaves substantial uncertainty as to whether, to what extent, and under what circumstances community-wide use of cloth face masks helps to reduce infection rates of SARS-CoV-2. The voluminous mechanistic evidence clearly demonstrates that masks reduce some measures of droplet transmission, such as the distance that larger droplets travel, and it is known that such droplets contain SARS-CoV-2. Images showing respiratory droplets expelled during sneezing or coughing have been used to elicit visceral reactions of the public, and a series of articles in the *New York Times* featured

---

[281] James M. Simmerman et al., *Findings from a Household Randomized Controlled Trial of Hand Washing and Face Masks to Reduce Influenza Transmission in Bangkok, Thailand: Household Randomized Controlled Trial of Hand Washing and Face Masks*, 2011 5 INFLUENZA & OTHER RESPIRATORY VIRUSES 256, 262 (2011).
[282] Chandini R. MacIntyre et al., *A Cluster Randomised Trial of Cloth Masks Compared with Medical Masks in Healthcare Workers*, 5 BMJ OPEN 1, 6 tbl.2 (2015).
[283] *Id.* at 2.

Virginia Tech professor Linsey Marr explaining in simple language how mask fibers "create a haphazard obstacle course through which air . . . must navigate," thus filtering the air.[284]

However, such surrogates of efficacy have not been demonstrated to correlate with infection outcomes, and therefore fail to show that masks reduce the true measure of interest, namely, the spread of respiratory illness. It is also not clear that these studies have adequately replicated real-world conditions even as to the surrogate of droplet transmission. Mannequin faces are unmoving and tend to be tested under conditions that generate particle sizes and air speeds that may not reflect the variable nature of human speech or breathing. For example, in a study co-authored by Linsey Marr, a constant rate of air flow was used, mannequin heads were placed in a chamber designed to minimize disruptions to air flow, and masks sometimes covered the mannequins' eyes.[285] Mannequins were also placed only 13 inches apart, relevant perhaps for crowded subway cars, but far closer than traditional conceptions of personal space would allow.[286] In real life it also is considered socially unacceptable to cough directly into someone's face at close range without at least averting the head or covering the cough. Although evidence is limited, one study comparing coughing into a mask versus the crook of the elbow demonstrated similar results in both the size and number of expelled droplets.[287]

Clinical evidence also fails to demonstrate that face masks are an effective intervention against the spread of respiratory illness. There have been 2 large-scale RCTs evaluating the use of facemasks at limiting the spread of SARS-CoV-2. One failed to show a statistically significant

---

[284] Katherine J. Wu, *One Mask Is Good. Would Two Be Better?*, *N.Y. Times*, Jan. 12, 2021, https://www.nytimes.com/2021/01/12/health/coronavirus-masks-transmission.html.
[285] Jin Pan, Charbel Harb, Weinan Leng & Linsey C. Marr, *Inward and Outward Effectiveness of Cloth Masks, a Surgical Mask, and a Face Shield*, , MEDRXIV 1, 16 (2021), https://www.medrxiv.org/content/10.1101/2020.11.18.20233353v1.full.pdf.
[286] Vikas Mehta, *The New Proxemics: COVID-19, Social Distancing, and Sociable Space*, 25 J. URBAN DESIGN 669 (2020) (noting that traditional notions of personal space span 4 to 12 feet for acquaintances).
[287] Gustavo Zayas et al., *Effectiveness of Cough Etiquette Maneuvers in Disrupting the Chain of Transmission of Infectious Respiratory Diseases*, 13 BMC PUB. HEALTH 1, 8 (2013).

benefit to those randomized to wear high-quality surgical masks in both the intention-to-treat and per protocol (i.e., excluding those who reported not wearing masks as specified in the protocol) analyses. The other failed to find a statistically significant benefit to cloth masks, but found an 11% relative reduction in COVID-19 prevalence for surgical masks that was marginally statistically significant, with the confidence interval spanning 0% to 22%. In the latter trial, absolute reductions in COVID-19-like illness associated with mask-wearing were only 1% (reduced from 8.6% in control villages to 7.6% in intervention villages), while absolute reductions in symptomatic seroprevalence were less than 0.1% (from 0.76% in control villages to 0.68% in intervention village), raising questions about whether resources devoted to mask production, awareness, utilization, and enforcement could be deployed to greater public health benefit if directed at alternate interventions, such as vaccination, contact-tracing, or isolation. This study also does not apply to children, as they were excluded, showed mask compliance waned drastically after the study period was complete, and may not extrapolate to settings disparate from rural Bangladesh, which at the time of this study had no available vaccination and very low rates of natural immunity.

In non-healthcare settings, of the 14 RCTs identified by the authors that evaluated face mask efficacy compared to no-mask controls in protecting against respiratory infections other than COVID-19, 13 failed to find statically significant benefits from facemask use under intention-to-treat analyses. In communal living settings, four of five RCTs failed to show statistically significant benefits to masking, and the promising results of the fifth study were not confirmed when its authors sought to replicate the results in a much larger follow-up trial. Of eight RCTs that evaluated face mask efficacy against respiratory illness transmission in non-healthcare household settings, all eight failed to find a statistically significant benefit for the use

of face masks alone compared to controls in their intention-to-treat analyses, and only three found statistically significant benefit in highly selective sub-group analyses (**Table 1**).

While there is observational evidence that facemasks protect against SARS-CoV-1 and SARS-CoV-2, especially in healthcare settings, this evidence is confounded by other variables. Study limitations and potential confounders are often stated by study authors, but tend to be truncated or omitted when study results are reported to the public.[288]

We are not the first to evaluate the body of available evidence regarding mask use and conclude that the evidence fails to clearly support a benefit from mask wearing. Of 16 quantitative meta-analytical analyses evaluating facemask use in non-healthcare, non-mass gathering settings, only two reported statistically significant benefits of facemask use alone compared to no-mask controls, and those results were largely due to inclusion of the observational SARS-CoV-1 data discussed above.

Some evidence suggests masks cause higher infection rates

Studies of other respiratory illnesses raise the possibility that masks could actually cause higher infection rates under some circumstances, although as with the evidence for masks in general, the existing evidence fails to clearly support this hypothesis and the point estimates of harm could simply be the result of chance. However, the explanation of chance is similarly applicable to the non-significant point estimates of benefit found in some studies, which have frequently been interpreted as supportive of mask efficacy on the rationale that the studies had insufficient statistical power.[289,290,291,292,293,294]

---

[288] Apoorva Mandavilli, *The Price for Not Wearing Masks: Perhaps 130,000 Lives*, N.Y. TIMES, Oct. 23, 2020, https://www.nytimes.com/2020/10/23/health/covid-deaths.html.

[289] Julii Brainard et al., *Community Use of Face Masks and Similar Barriers to Prevent Respiratory Illness Such as COVID-19: A Rapid Scoping Review*, 25 EUROSURVEILLANCE 1, 12 (2020).

[290] Chandini R. MacIntyre & Abrar A. Chughtai, *A Rapid Systematic Review of the Efficacy of Face Masks and Respirators Against Coronaviruses and Other Respiratory Transmissible Viruses for the Community, Healthcare Workers and Sick Patients*, 104 INT'L J. NURSING STUDIES 1, 4 (2020).

The World Health Organization has noted the possibility that mask wearing could accelerate disease spread by providing a false sense of security that induces individuals to forego standard sanitary measures,[295] although this concern is contested[296] and the evidence is mixed. In one study, mask wearing was associated with reductions of physical distancing when the experimenter asked passersby for directions, particularly if the experimenter was wearing clothes suggestive of high social status,[297,298] Another study, however, have found passersby increased distance from an experimenter standing on the side of a pathway if the experimenter was wearing a mask, particularly if the mask was homemade and accompanied by goggles.[299]

Mask use could also lead to higher infection rates by encouraging other behavioral changes, such as by providing perceived license to engage in high-risk activities. As with physical distancing, the evidence is mixed. In the United States, a review of location data aggregated from multiple phone apps found that mask mandates were associated with 20-30 minutes of increased daily time outside the home and increase restaurant visitation,[300] while in

---

[291] Chandini R. MacIntyre et al., *Cluster Randomised Controlled Trial to Examine Medical Mask Use as Source Control for People with Respiratory Illness*, 6 BMJ OPEN 1, 6 (2016).
[292] Mandy Wang et al. *A Cluster-Randomised Controlled Trial to Test the Efficacy of Facemasks in Preventing Respiratory Viral Infection Among Hajj Pilgrims*, 5 J. EPIDEMIOLOGY & GLOBAL HEALTH 181, 182 (2015).
[293] Laetitia Canini et al., *Surgical Mask to Prevent Influenza Transmission in Households: A Cluster Randomized Trial*, 5 PLOS ONE 1, 5 (2010).
[294] Allison E. Aiello et al., *Facemasks, Hand Hygiene, and Influenza Among Young Adults: A Randomized Intervention Trial*, 7 PLOS ONE 1, 7 (2012).
[295] *Advice on the Use of Masks [in] the Community, During Home Care and in Health Care Settings in the Context of the Novel Coronavirus (2019-Ncov) Outbreak: Interim Guidance*, WORLD HEALTH ORG., Jan. 29, 2020, at 1, https://apps.who.int/iris/handle/10665/330987 (last visited Sep. 5, 2021).
[296] Eleni Mantzari et al., *Is Risk Compensation Threatening Public Health in the Covid-19 Pandemic?*, 370 BMJ m2913 (2020).
[297] Martin Aranguren, *Face Mask Use Conditionally Decreases Compliance With Physical Distancing Rules Against COVID-19: Gender Differences in Risk Compensation Pattern*, ANNALS BEHAVIORAL MED. (2021), https://doi.org/10.1093/abm/kaab072.
[298] *See also* Alice Cartaud et al., *Wearing a Face Mask Against COVID-19 Results in a Reduction of Social Distancing*, 15 PLOS ONE 1, 1 (2020) (online experiment in which subjects must assess whether the distance to a happy, angry, neutral, or masked virtual character is appropriate).
[299] Massimo Marchiori, *COVID-19 and the Social Distancing Paradox: Dangers and Solutions*, ARXIV 1, 6 (2020), https://arxiv.org/pdf/2005.12446.
[300] Youpei Yan et al., *Do Face Masks Create a False Sense of Security? A COVID-19 Dilemma*, MEDRXIV 1, 16 (2020), https://www.medrxiv.org/content/10.1101/2020.05.23.20111302v2.full.pdf.

Germany a review of Google's location data showed small reductions in visits to grocery stores and small decreases in time spent outside the home following mask mandates.[301] Both studies relied on mask mandates rather than actual mask wearing, and neither used randomization nor measured physical distancing.

Even if masks do not affect individual behavior choices for ordinary activities such as visiting grocery stores or working from home, they could lower social inhibitions for engaging in potentially high-risk outlier events such as political rallies, civic demonstrations, professional conferences, and sporting events.[302] They could also provide businesses and government leaders with political cover to "reopen the economy safely," including the reopening of restaurants, bars, health facilities, schools, and other locations where large numbers of people congregate.

Masks could also accelerate disease spread in other ways. For example, the auditory difficulties engendered by masks combined with their obfuscation of lip movements could cause wearers to talk more loudly (which yields greater numbers of droplets[303]), lean to the side of plastic barriers while speaking, or approach more closely to hear or be heard, undermining the reductions in droplet movement that masks provide. This concern is particularly relevant for the aged or others who have impaired hearing and who may also be at higher risk of severe COVID-19 infection.[304] Although masks appear to reduce the distance traveled by larger droplets, one

---

[301] Roxanne Kovacs et al., *Compulsory Face Mask Policies Do Not Affect Community Mobility in Germany*, ECONSTOR WORKING PAPER (2020), http://hdl.handle.net/10419/218945 (last visited Aug. 9, 2021).
[302] William F. Maloney & Temel Taskin, *Determinants of Social Distancing and Economic Activity During COVID-19: A Global View*, WORLD BANK POL'Y RESEARCH WORKING PAPER 1, 11 (2020) ("[W]earing masks makes individuals feel more in control and protected and hence, the net impact is to increase mobility.").
[303] Phillip Anfinrud et al., *Visualizing Speech-Generated Oral Fluid Droplets with Laser Light Scattering*, 382 NEW ENG. J. MED. 2061, 2062 (2020).
[304] Joshua Chodosh et al., *Face Masks Can Be Devastating for People with Hearing Loss*, 370 BMJ 1, 1 (2020).

study found that neck gaiter-type masks can disperse large droplets into a multitude of smaller droplets, which the authors noted "might be counterproductive."[305]

Increased facial touching is also a concern.[306] In one study, 75% of participants reported mask discomfort,[307] and another study reported that 20% of mask wearers experience facial itch,[308] both of which may lead to increased facial touching. Although some studies have reported decreased facial touching associated with mask wearing, these studies had important limitations, such as lacking randomization and blinding,[309] not including indoor spaces,[310] and excluding subjects who touched their faces to don, doff, or adjust their masks.[311]

Contamination of the hands can occur when masks are removed or reused.[312,313] Mask studies may therefore overestimate mask benefit and underestimate harm, since most provide subjects with fresh masks at frequent intervals, sometimes including multiple masks per day.[314,315] By contrast, it is unclear how often cloth masks are washed during community use, leading to the possibility that they are inadvertently serving as homemade disease cultures with

---

[305] Emma P. Fischer et al., *Low-Cost Measurement of Face Mask Efficacy for Filtering Expelled Droplets During Speech*, 6 SCI. ADVANCES 1, 3 (2020).
[306] Terri Rebmann et al., *Physiologic and Other Effects and Compliance with Long-term Respirator Use Among Medical Intensive Care Unit Nurses*, 41 AM. J. INFECTION CONTROL 1218 (2013).
[307] Laetitia Canini et al., *Surgical Mask to Prevent Influenza Transmission in Households: A Cluster Randomized Trial*, 5 PLOS ONE 1, 5 (2010).
[308] Jacek C. Szepietowski et al., *Face Mask-induced Itch: A Self-questionnaire Study of 2,315 Responders During the COVID-19 Pandemic*, 100 ACTA DERMATO-VENEREOLOGICA 1, 2 fig.1 (2020).
[309] Tiffany L. Lucas, *Frequency of Face Touching With and Without a Mask in Pediatric Hematology/oncology Health Care Professionals*, 67 PEDIATRIC BLOOD & CANCER e28593 (2020).
[310] Yong-Jian Chen et al., *Comparison of Face-Touching Behaviors Before and During the Coronavirus Disease 2019 Pandemic*, 3 JAMA NETWORK OPEN e2016924 (2020).
[311] Lasse S. Liebst et al., *Face-touching Behaviour as a Possible Correlate of Mask-Wearing: A Video Observational Study of Public Place Incidents During the COVID-19 Pandemic*, TRANSBOUNDARY & EMERGING DISEASES (2021), https://pubmed.ncbi.nlm.nih.gov/33817991/ (online ahead of print).
[312] Tyler M. Brady et al., *Transfer of Bacteriophage MS2 and Fluorescein from N95 Filtering Facepiece Respirators to Hands: Measuring Fomite Potential*, 14 J. OCCUPATIONAL & ENVTL. HYGIENE 898, 904 (2017).
[313] Lisa Casanova et al., *Virus Transfer from Personal Protective Equipment to Healthcare Employees' Skin and Clothing*, 14 EMERGING INFECTIOUS DISEASES 1291, 1292–93 (2008).
[314] E.g., Allison E. Aiello et al., *Facemasks, Hand Hygiene, and Influenza Among Young Adults: A Randomized Intervention Trial*, 7 PLOS ONE 1, 2 (2012).
[315] E.g., Mohammad Alfelali et al., *Facemask Against Viral Respiratory Infections Among Hajj Pilgrims: A Challenging Cluster-Randomized Trial*, 15 PLOS ONE 1, 4 (2020).

the potential to contaminate surfaces when they are temporarily removed. Clean masks can come in contact with contaminated surfaces such as restaurant tables, bathroom shelving, handbag contents, or coat pockets and then be placed on the face.[316,317] For healthy individuals, the dampness of an otherwise clean cloth mask may increase the likelihood of contact contamination and the need for mask adjustment.

VIII. Conclusion

We reviewed the mechanistic, observational, and clinical evidence relevant to the use of cloth face masks in community settings to limit the spread of respiratory infections, and in particular the novel SARS-CoV-2 coronavirus. In each area, we found existing evidence inadequate to demonstrate clear benefit (or harm). Mechanistic evidence shows a clear benefit as measured by laboratory surrogates, but it is not clear to what extent those surrogates are relevant to the clinical question of infection rate or offset by behavioral factors. Uncontrolled observational studies are confounded by numerous known and unknown variables, and most considered mask mandates or self-reported mask wearing as the key variable rather than actual mask usage. The infection dynamics of SARS-CoV-2 differ from SARS-CoV-1 and other respiratory illnesses, meaning that much of the evidence, even if suggestive, has uncertain relevance to SARS-CoV-2. Recommendations to impose mask mandates based on the precautionary principle fail to account for the possibility that masks cause harm,[318] or that masks may have varying benefits and risks in different settings.

Notwithstanding the lack of evidence, in the midst of a pandemic policymakers and public health officials cannot wait until high-quality evidence is generated. However, if they

---

[316] Nikolaos I. Stilianakis & Yannis Drossinos, *Dynamics of Infectious Disease Transmission by Inhalable Respiratory Droplets*, 7 J. ROYAL SOC'Y INTERFACE 1, 1 (2010).
[317] Alex W. Chin et al., *Stability of SARS-CoV-2 in Different Environmental Conditions*, 1 LANCET MICROBE e10 (2020).
[318] Trisha Greenhalgh et al., *Face Masks for the Public During the COVID-19 Crisis*, 369 BMJ 1 (2020).

determine based on limited evidence that community masking policies are appropriate, it is an ethical imperative to refrain from portraying the evidence as stronger than it actually is. Estimates of lives that could potentially be saved, if provided, must be carefully balanced with appropriate disclosure of study limitations and uncertainties. Some models supporting community face masking suggest large beneficial effects,[319,320] but these models are based on assumptions that face masks reduce SARS-CoV-2 transmission by 40–50%[321,322,323]— assumptions that are not adequately supported by existing data. More generally, given the low quality of evidence, the absence of statistically significant benefit indicated by most randomized controlled trials, and the possible harm suggested by a few studies, scientists and public health officials must take care not to apply a double standard to available studies—emphasizing projections of lives saved when evidence suggests benefit, while focusing on study limitations rather than outcomes when the evidence suggests harm or the absence of benefit.

Overconfident portrayal of evidence could also stifle research agendas, making it difficult to reevaluate previously-held but insufficiently supported positions.[324,325] Early in the pandemic, pressure exerted on public officials to offer immediate solutions led to rhetoric that outpaced the evidence. Once officials or others became publicly committed to a position on masks, it became difficult to advocate for high-quality evidence generation, leading to a situation in which, despite

---

[319] Steffen E. Eikenberry et al., *To Mask or Not to Mask: Modeling the Potential for Face Mask Use by the General Public to Curtail the COVID-19 Pandemic*, 5 INFECTIOUS DISEASE MODELLING 293, 296 (2020).
[320] Richard Stutt et al., *A Modelling Framework to Assess the Likely Effectiveness of Facemasks in Combination with 'Lock-Down' in Managing the COVID-19 Pandemic*, 476 PROCEEDINGS ROYAL SOC'Y 1, 2 (2020).
[321] Emmanuela Gakidou et al., *Global Projections of Potential Lives Saved from COVID-19 Through Universal Mask Use*, MEDRXIV 1, 16 fig.2 (2020), https://www.medrxiv.org/content/10.1101/2020.10.08.20209510v2.full.pdf.
[322] IHME Covid Forecasting Team, *Modeling COVID-19 Scenarios for the United States*, 27 NATURE MED. 94, 95 (2021).
[323] Tatiana Filonets et al., *Investigation of the Efficiency of Mask Wearing, Contact Tracing, and Case Isolation During the COVID-19 Outbreak*, 10 J. CLINICAL MED. 1, 5 (2021).
[324] Dyani Lewis, *COVID-19 Rarely Spreads Through Surfaces. So Why Are We Still Deep Cleaning?*, 590 NATURE 26, 26 (2021).
[325] *Science Brief: SARS-CoV-2 and Surface (Fomite) Transmission for Indoor Community*, CTRS. FOR DISEASE CONTROL & PREVENTION, https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/surface-transmission.html (last visited Apr. 20, 2020).

the prevalence of masking policies, only two randomized trials have been performed to address the question of face mask efficacy for SARS-CoV-2. Until it is clear whether and in what circumstances masks provide net benefit (or cause net harm), ethical concerns should not foreclose Institutional Review Boards from approving trials that are randomized, blinded, and controlled. Reliance on randomized evidence is not only a common practice for other clinical interventions[326] (there have been at least 28 randomized controlled trials around the world of hydroxychloroquine, for example[327]), but is a fundamental point of distinction between modern medicine and that of centuries past.

The well-known distinction between absence of evidence and evidence of absence applies to the COVID-19 context.[328] If face masks save lives—or even if it is reasonably likely that they do—such measures are appropriate and compassionate. Simultaneously, higher quality evidence can be gathered. This rationale applies to all unproven interventions, and has served as a basis for the FDA's expanded access program and the various Right-to-Try laws.[329] Yet as with medicines, the use of unproven non-drug technologies is not without potential harm. Users of the technology can acquire a false sense of security that causes the substitution of unproven or less effective measures for measures for which better evidence may be available, such as physical distancing, improved indoor ventilation, and vaccination.[330] If later evidence proves the intervention useless or harmful, the experience can undermine public trust.[331] The technology

---

[326] Margaret McCartney, *We Need Better Evidence on Non-drug Interventions for COVID-19*, 370 BMJ 1, 1 (2020).
[327] Cathrine Axfors et al., *Mortality Outcomes with Hydroxychloroquine and Chloroquine in COVID-19: An International Collaborative Meta-Analysis of Randomized Trials*, 12 NATURE COMMC'NS 1, 1 (2021).
[328] Shuo Feng et al., *Rational Use of Face Masks in the COVID-19 Pandemic*, 8 LANCET RESPIRATORY MED. 434, 435 (2020).
[329] *See generally* Jonathan J. Darrow et al., *Practical, Legal, and Ethical Issues in Expanded Access to Investigational Drugs*, 372 NEW ENG. J. MED. 279 (2015) (describing the FDA's expanded access program).
[330] Graham P. Martin et al., *Science, Society, and Policy in the Face of Uncertainty: Reflections on the Debate Around Face Coverings for the Public During COVID-19*, 30 CRITICAL PUB. HEALTH 1, 1 (2020).
[331] Brit Trogen et al., *Adverse Consequences of Rushing a SARS-CoV-2 Vaccine: Implications for Public Trust*, 323 J. AM. MED. ASS'N 2460, 2460 (2020).

itself may cause harm through mechanisms that are not yet well understood, or cause economic, environmental or other harms that indirectly impact health. For example, although masks are individually inexpensive, the collective costs of producing and distributing an adequate and continuous supply of masks to a global community of 7.8 billion people is not trivial, nor are the environmental harms that result when they are discarded.[332,333]

More than a century after the 1918 influenza pandemic, examination of the efficacy of masks has produced a large volume of mostly low- to moderate-quality evidence that has largely failed to demonstrate their value in most settings. Ideally, high-quality evidence will eventually provide clarification. When repeated attempts are undertaken to demonstrate an expected or desired outcome, there is a risk of declaring the effort resolved once results consistent with preconceived notions are generated, regardless of the number or extent of previous failures. Scientists and public health officials should exercise caution to ensure that this potential bias does not lead to a cessation of research once the first high-quality study demonstrating mask efficacy is reported.

---

[332] Kajanan Selvaranjan et al., *Environmental Challenges Induced by Extensive Use of Face Masks During COVID-19: A Review and Potential Solutions*, 3 ENVTL. CHALLENGES 100039 (2021).
[333] V.C. Shruti et al., *Reusable Masks for COVID-19: A Missing Piece of the Microplastic Problem During the Global Health Crisis*, 161 MARINE POLLUTION BULL. 111777 (2020).

Table 1. RCT evidence for the efficacy of face masks against respiratory virus transmission.

	Authors (Year) [Context]	Intention-To-Treat (ITT) Outcomes [Statistical Significance in ITT Outcome]	Selected Secondary Outcomes
1	Aiello et al.[334] (2010) [U. Mich. dorms]	Influenza-like illness (ILI) was cumulatively reported in 26.2% (99/378) of the mask group, 25.1% (92/367) of mask plus hand hygiene (HH), and 32.1% (177/552) of controls. Neither group's reductions were statistically significant before (mask v. control, P=.25; mask plus HH, P=.10) or after adjustment for covariates (mask v. control, P=.19; mask plus HH, P=.08). [Statistical Significance: No]	Reported statistically significant point reductions in adjusted ILI for both mask and mask + HH groups compared to controls in study weeks 3-6 (RRs of 0.49–0.72 with P values from 0.01–0.05).
2	Aiello et al.[335] (2012) [U. Mich. dorms]	ILI was cumulatively reported in 11.7% (46/392) of the mask group, 8.9% (31/349) of mask plus hand hygiene (HH), and 13.8% (51/370) of controls. Neither group's reductions were statistically significant before (mask v. control. P=.52; mask plus HH, P=.10) or after adjustment for covariates (mask v. control, P=.42; mask plus HH, P=.13). [Statistical Significance: No]	Like the 2010 study, reported statistically significant point reductions in adjusted ILI for the mask + HH group compared to controls in study weeks 3-6 (RRs of 0.25–0.40 with P values from 0.01–0.03). However, no statistically significant point reductions were reported for the mask group only.
3	Abdin et al.[336] (2005) [Hajj pilgrims]	Study of acute respiratory infection (ARI) in 995 Hajj pilgrims with a compliance rate of 81% in its health education plus face mask arms found "no association [ ] observed between compliance with face mask wearing and developing ARI, (OR 0.97, 95% CI 0.73-1.28)." [Statistical Significance: No]	N/A
4	Barasheed et al.[337] (2014) [Hajj pilgrims]	Pilot study that reported 53% (28/53) of masked contacts who slept next to known sick patients subsequently developed ILIs compared to 31% (11/36) of masked contacts (P=0.04). [Statistical Significance: Yes]	Reported a statistically significant decrease in ILIs among the subgroup of masked contacts who reported wearing their masks >8 hours/day (P=0.01) compared to both controls and contacts who reported mask use <8 hours/day.
5	Alfelali et al.[338] (2020) [Hajj Pilgrims]	Follow-up study to Barasheed et al.'s pilot RCT above; reported no statistically significant difference in viral respiratory infections (VRIs) among masked tents (41.6%, 149/358) compared to control tents (43.8%, 128/292; P=.18). [Statistical Significance: No]	In a per-protocol analysis (that only considered daily mask wearers in the intervention group and non-mask wearers in the control group), failed to find statistically significant differences "against laboratory-confirmed viral respiratory infections (OR

[334] Allison E. Aiello et al., *A Randomized Intervention Trial of Mask Use and Hand Hygiene to Reduce Seasonal Influenza-Like Illness and Influenza Infections Among Young Adults in a University Setting*, 14 INT'L J. INFECTIOUS DISEASES 491, 495-6 (2010).

[335] Allison E. Aiello et al., *Facemasks, Hand Hygiene, and Influenza Among Young Adults: A Randomized Intervention Trial*, 7 PLOS ONE 1, 6 tbls.3, S1, and S5 (2012).

[336] Ebtihal Z. Abdin et al., *Effect of Use of Face Mask on Hajj-Related Respiratory Infection Among Hajjis from Riyadh: A Health Promotion Intervention Study*, 12 SAUDI EPIDEMIOLOGY BULL. 27, 27–28 (2005).

[337] Osamah Barasheed et al., *Pilot Randomised Controlled Trial to Testing Facemasks Effectiveness in Preventing Influenza-Like Illness Transmission Among Hajj Pilgrims,* 14 INFECTIOUS DISORDERS DRUG TARGETS 110, 113 tbl.1 (2014).

[338] Mohammad Alfelali et al., *Facemask Against Viral Respiratory Infections Among Hajj Pilgrims: A Challenging Cluster-Randomized Trial*, 15 PLOS ONE 1, 7 (2020).

			1.2, 95% CI 0.9–1.7, p = 0.26) nor against clinical respiratory infection (OR 1.3, 95% CI 1.0–1.8, p = 0.06)."
6	Canini et al.[339] (2010) [Households in France]	Study where index cases in households wore surgical masks for five days following diagnosis; reported secondary ILI case rates of 16.2% (24/148) in the mask group versus 15.8% (25/158) in the control group with no statistical difference (P=1.00). [Statistical Significance: No]	Also reported no decreases in ILIs in households where masks were worn within 24 hours of symptom onset, (18.1% (15/83) masked vs. 15.7% (7/108) control; P=0.70) and found no association between various measures of mask adherence and incidence of ILI among household contacts (P=0.098–0.31).
7	Macintyre et al.[340] (2009) [Households in Australia]	Reported no significant differences between surgical or P2 (N95 equivalent) masks for secondary ILI infection rates at the individual (surgical mask: 20% (19/94), P=0.46; P2 mask: 15% (14/92), P=1.0; control: 16% (16/100)) or household levels (surgical mask: 32% (15/47), P=0.50; P2 mask: 22% (10/46), P=0.81; control: 24% (12/50)). [Statistical Significance: No]	Per-protocol analysis found a statistically significant decrease (RR: 0.26, P=.015) in infection rates among adherent mask users but adherence was low (only 38% (36/94) of surgical and 46% (42/92) of P2 mask users reported wearing masks "most or all" of the time on the intervention's first day).
8	Macintyre et al.[341] (2016) [Households in China]	Study where index cases in households wore surgical masks for seven days following diagnosis, using three different primary outcomes: clinical respiratory illness (CRI), lab-confirmed viral infection (LCVI), and influenza-like illness (ILI). Reported lower outcome rates for masked groups in all outcomes, with none reaching statistical significance. For CRI, mask group rates of 0.19% (4/2098) versus 0.29% (6/2036) for controls (RR: 0.65, 95% CI 0.18–2.29). For LCVI, mask group rates of 0.05% (1/2098) versus 0.05% (1/2036) for controls (RR: 0.97, 95% CI .06–15.5). For ILI, mask group rates of 0.05% (1/2098) versus 0.15% (3/2036) for controls (RR: 0.03–3.11). [Statistical Significance: No]	In a per-protocol analysis, reported a statistically significant hazard ratio (HR) decrease for CRIs in masked groups (HR: 0.22, 95% CI 0.06–0.86), but not for ILIs (HR: 0.18, 0.02–1.73) or LCVIs (HR: 0.11, 95% CI 0.01–4.40).
9	Simmerman et al.[342] (2011) [Households in Thailand]	Reported no statistically significant differences on lab-confirmed, intra-household secondary influenza infection between handwashing (23%, 66/292), handwashing plus masks (23%, 66/291), and control groups (19%, 58/302; 3-group adjusted Chi-square: 0.63). Using ILI secondary attack rate as a primary measure, reported increases in ILI rates in handwashing (17%, 50/292) and handwashing plus mask groups (18%, 51/291) compared to controls (9%, 26/302; 3-group adjusted Chi-square: 0.01). [Statistical Significance: No]	None notable.
10	Cowling et al.[343]	Reported no statistically significant benefit on intra-	Reported no statistically significant

[339] Laetitia Canini et al., *Surgical Mask to Prevent Influenza Transmission in Households: A Cluster Randomized Trial*, 5 PLOS ONE 1, 5 (2010).

[340] Chandini R. MacIntyre et al., *Face Mask Use and Control of Respiratory Virus Transmission in Households*, 15 EMERGING INFECTIOUS DISEASES 233, 238 tbl.4 (2009).

[341] Chandini R. MacIntyre et al., *Cluster Randomised Controlled Trial to Examine Medical Mask Use as Source Control for People with Respiratory Illness*, 6 BMJ OPEN 1, 5–7, tbl. 2, 4 (2016).

[342] James M. Simmerman et al., *Findings from a Household Randomized Controlled Trial of Hand Washing and Face Masks to Reduce Influenza Transmission in Bangkok, Thailand: Household Randomized Controlled Trial of Hand Washing and Face Masks*, 5 INFLUENZA & OTHER RESPIRATORY VIRUSES 256, 263 tbl.2 (2011).

	(2008) [Households in Hong Kong]	household secondary influenza infection rates when all household contacts wore masks (5.9%, 12/205) or were educated and given hand hygiene materials (6.6%, 4/61), compared to controls (6.0%, 5/84; P=0.99). Also found no differences (P=0.52–1.0) using three different clinical definitions of influenza. [Statistical Significance: No]	variation in secondary infection rates when interventions were implemented within 36 hours of symptom onset using lab or clinical influenza diagnostic criteria (P=0.44–0.69).
11	Cowling et al.[344] (2009) [Households, /Hong Kong]	Follow-up study of Cowling et al. (2008) above; reported no statistically significant benefit for PCR-confirmed secondary influenza infections when all household contacts wore masks and practiced hand hygiene ("MH"; 7.0%, 18/258) compared to hand hygiene alone ("HH"; 5.4%, 14/257), or a control arm with neither intervention (10.0%, 28/279; 3-group P value: 0.22). Also found no differences using two different clinical diagnostic criteria (3-group P-values of 0.40 and 0.28). [Statistical Significance: No]	In a pre-planned, sub-group analysis of households that implemented interventions within 36 hours of symptom onset, 3-group P values reported statistically significant differences under two of three illness criteria, although the MH group still underperformed the HH-alone group in most cases (PCR-confirmed: HH 5.4% (7/130), MH 4.0% (6/149); Clinical Definition 1: HH 10.8% (14/130), MH 18.1% (27/149); Clinical Definition 2: HH 3.1% (4/130), MH 4.7% (7/149)).
12	Suess et al.[345] (2007) [Households in Germany]	Reported no statistically significant differences, with lab-confirmed secondary infection rates of 9% (6/69) in the mask, 15% (10/67) in the mask plus hand hygiene (MH), and 23% (19/82) in the control group (P=0.18), and secondary clinical ILI rates of 9% (6/69) in the mask, 9% (6/67) in the MH group, and 17% (14/82) in controls (P=0.37). [Statistical Significance: No]	In a per-protocol analysis, found a statistically significant decrease in the OR of the masked group compared to controls (OR: 0.3, P=0.04) in lab-confirmed influenza, but not clinical ILI cases (OR: 0.5, P=0.3).
13	Larson et al.[346] (2010) [Households in New York City]	Reported unadjusted secondary URI/ILI/influenza rates of 0.137 for education, 0.144 for education plus hand sanitizer (HS), and 0.124 for education plus mask plus hand sanitizer (MHS) with no reported P values, but "a significant decrease... [in MHS] compared with the Education group." In the primary multivariate regression analysis, found "no significant differences in rates of infection by intervention group" with P values ranging from 0.19–0.89. [Statistical Significance: No]	In a secondary adjusted model, reported intervention group as significantly impacting infection rate with a 3-group P value of 0.02 between the MHS group (OR: 0.82; 95% CI 0.70-0.97), the HS alone group (OR: 1.01; 95% CI 0.85-1.21), and the educational reference group.
14	Jacobs et al.[347] (2009) [Hospital workers in Japan]	Reported no statistically significant difference between mean number of days of cold symptoms reported by surgical face mask wearers (mean=16.1 days) and non-wearers (mean=14.3 days; P=0.81) during the winter season. [Statistical Significance: No]	In a univariate analysis, reported the only significantly predictive factor of mean days with cold symptoms was living with children under 16 years old (P=0.02).

[343] Benjamin J. Cowling et al., *Preliminary Findings of a Randomized Trial of Non-pharmaceutical Interventions to Prevent Influenza Transmission in Households*, 3 PLOS ONE 1, 7 tbl.2 (2008).
[344] Benjamin J. Cowling et al., *Facemasks and Hand Hygiene to Prevent Influenza Transmission in Households: A Cluster Randomized Trial*, 151 ANNALS INTERNAL MED. 437, 442 tbl.3 (2009).
[345] Thorsten Suess et al., *The Role of Facemasks and Hand Hygiene in the Prevention of Influenza Transmission in Households: Results from a Cluster Randomised Trial; Berlin, Germany, 2009–2011*, 12 BMC INFECTIOUS DISEASES 1, 10 tbl.5 (2012).
[346] Elaine L. Larson et al., *Impact of Non-pharmaceutical Interventions on URIs and Influenza in Crowded, Urban Households*, 125 PUB. HEALTH REP. 178, 185-6 tbls.4-5 (2010).
[347] Joshua L. Jacobs et al., *Use of Surgical Face Masks to Reduce the Incidence of the Common Cold Among Health Care Workers in Japan: A Randomized Controlled Trial*, 37 AM. J. INFECTION CONTROL 417, 419 tbl.3 (2009).

15	Bundgaard et al.[348] (2021) [adult community members in Denmark]	The primary outcome of SARS-CoV-2 infection (either laboratory-confirmed, or a hospital-based diagnosis) occurred in 42 (1.8%) of 2392 participants in the mask group and 53 (2.1%) of 2470 in the control group (P=0.38). [Statistical Significance: No]	Nine participants (0.5%) were positive for at least 1 of the 11 respiratory viruses other than SARS-CoV-2, compared with 11 participants (0.6%) in the control group (P=0.87).
16	Abaluck et al. (2021) [cluster-randomized communities in Bangladesh]	The primary outcome of symptomatic SARS-CoV-2 seroprevalence was 0.76% in control villages and 0.68% in intervention (i.e., both cloth and surgical mask) villages. [Statistical Significance: Yes]	Excluding surgical mask villages, symptomatic SARS-CoV-2 seroprevalence was 0.76% in control villages and 0.74% in cloth mask villages (P=0.54)

[348] Henning Bundgaard et al., *Effectiveness of Adding a Mask Recommendation to Other Public Health Measures to Prevent SARS-CoV-2 Infection in Danish Mask Wearers: A Randomized Controlled Trial*, 174 ANNALS INTERNAL MED. 335 (2021).

Table 2. Quantitative meta-analytical evidence for the efficacy of community masking against respiratory viral infections.

Authors Year	Total studies [non-healthcare settings] (RCTs) Key findings	[characterization] Supporting text
Gómez-Ochoa et al.[349] 2021	5 [5] (5) Brief letter to the editor that reanalyzed the data from the Chaabna et al. meta-analysis, but only included studies that used face mask use alone compared against a control group. The authors found no significant differences between medical facemasks use only and controls in the odds of developing laboratory-confirmed influenza (9.6% (27/274) vs. 9.7% (50/515)) and influenza-like illness (13.7% (58/423) vs. 14.9% (100/673)).	[critical] "Because of these divergent results and the lack of high-quality research…, strong recommendations for facemask use in the community context should be issued with caution…."
Aggarwal et al.[350] 2020	9 [9] (9) Using results from 9 non-healthcare RCTs, found that mask use, both with hand hygiene (P=.714) and without (P=.226), was not associated with lower rates of ILI infection in community settings.	[equivocal] "Available evidence does not confirm a protective effect of face mask usage alone in a community setting against influenza-like illnesses (and potentially, the COVID-19)."
Brainard et al.[351] 2020	31 [16] (12) Did not report any statistically significant results when analyzing RCT data. Reported that mask use was not associated with statistically significant reductions in ILIs when used by a well person (11.2% (116/1032) vs. 12.1% (127/1046), P=.68), when used as source control by an ill person in a home setting (5.6% (25/450) vs. 6.2% (28/453), P=.87), or when used by all parties in a home with a sick individual (11.0% (79/715) vs. 12.0% (107/890), P=.43). Authors reported significant reductions in multiple observational study types including cross-sectional (22.3% (2771/12418) vs. 34.1% (7287/21353), P=.003), case-control (18.4% (128/694) vs. 40.5% (327/807), P=.02), and pre-post (3.3% (15/454) vs. 10.3% (95/920), P<.001), but not in cohort studies (13.8% (248/1795) vs. 20.4% (640/3131), P=.52).	[supportive] "The quality of the evidence is problematic. . . [o]ur best estimate is that the effect of wearing a face mask is between the effects seen in RCTs and the effects seen in cohort studies, or around 6 to 15% reduction in disease transmission."[352]

[349] Sergio A. Gómez-Ochoa & Taulant Muka, *Meta-Analysis on Facemask Use in Community Settings to Prevent Respiratory Infection Transmission Shows No Effect*, 103 INT'L J. INFECTIOUS DISEASE 257, 257 (2021).

[350] Nishant Aggarwal et al., *Facemasks for Prevention of Viral Respiratory Infections in Community Settings: A Systematic Review and Meta-Analysis*, 103 INDIAN J. PUB. HEALTH S192, S198 (2020).

[351] Julii Brainard et al., *Community Use of Face Masks and Similar Barriers To Prevent Respiratory Illness Such As COVID-19: A Rapid Scoping Review*, 25 EUROSURVEILLANCE 1, 1 (2020).

[352] A pre-print version of the paper concluded that evidence was "not sufficiently strong to support widespread use of facemasks as a protective measure against COVID-19," but this conclusion was changed in the final version to simply state that "[s]tudies specifically addressing COVID-19 infection are required." *See* Julii S. Brainard et al., *Facemasks and Similar Barriers to Prevent Respiratory Illness Such as COVID-19: A Rapid Systematic Review*, MEDRXIV 1, 1 (2020), https://www.medrxiv.org/content/10.1101/2020.04.01.20049528v1.full.pdf.

Chaabna et al.[353] 2020	12 [12] (10) Reported a significant protective effect of medical facemask use when evaluated in conjunction with other interventions (e.g. handwashing) (6.8% (273/4029) vs. 9.8% (458/4677), 95% CI 0.54–0.81). Did not report data for facemask use alone compared to control groups.	[supportive] "There is no available direct evidence in humans . . . for recommending cloth facemask use" but "[o]verall… there is enough evidence to show that medical facemasks are effective in community settings…."
Chu et al.[354] 2020	172 [3] (0) Using data from six observational studies on SARS-CoV-1, reported a statistically significant reduction in infections associated with face masks (adjusted OR: 0.33) compared to no mask controls. Four of the studies were in healthcare settings and one of the studies reported aerosol generating procedures. In a separate analysis, the authors reported statistical reductions in non-health-care settings on the basis of three observational studies from the SARS-CoV-1 epidemic (15.2% (37/244) vs. 21.0% (101/481); OR: 0.56).	[supportive] "[D]irect evidence is limited" but "[t]he use of face masks was protective for both healthcare workers and people in the community . . . , with both the frequentist and Bayesian analyses lending support to face mask use irrespective of setting . . . .
Jefferson et al.[355] 2020	15 [7] (15) Analyzing 15 RCTs, found no reductions in ILIs (RR 0.93, 95% CI 0.83-1.05) or influenzas (RR 0.84, 95% CI 0.61-1.17) for masks in the general population or healthcare workers (RR 0.37, 95% CI 0.05-2.50).	[equivocal] "We are uncertain whether wearing masks or N95/P2 respirators helps to slow the spread of respiratory viruses."
Liang et al.[356] 2020	21 [8] (6) Using data from both observational and RCT studies, the authors reported a significant protective effect on lab-confirmed respiratory viral infection (5.9% (307/5217) vs. 12.1% (419/3469), P<.00001). In non-healthcare settings, using RCT and observational data, the authors reported statistically significant effects (6.1% (111/1812) vs. 11.3% (227/2008), P=.002) with moderate heterogeneity between the studies (I^2=45%, P=.08). The authors did not consider RCT-only data, although if they had, between-group differences would have declined (5.4% (44/816) vs. 7.8% (77/989)).	[supportive] "The present systematic review and meta-analysis showed the general efficacy of masks in preventing the transmission of RVIs [respiratory viral infections]."
Ollila et al.[357] 2020	5 [5] (5) Analyzing data from 5 RCTs, reported strong and statistically significant results in favor of face mask	[supportive] "[Four] out of 17 studies supported the use of masks in the intention-to-treat

[353] Karima Chaabna et al., *Facemask Use in Community Settings to Prevent Respiratory Infection Transmission: A Rapid Review and Meta-Analysis,* 104 INT'L J. INFECTIOUS DISEASE 198, 205 (2021).

[354] Derek K. Chu et al., *Physical Distancing, Face Masks, and Eye Protection to Prevent Person-to-Person Transmission of SARS-CoV-2 and COVID-19: A Systematic Review and Meta-Analysis*, 395 LANCET 1973, 1984 (2021).

[355] Tom Jefferson et al., *Interventions for the Interruption or Reduction of the Spread of Respiratory Viruses*, 7 COCHRANE DATABASE SYS. REV. 1, 108 (2011).

[356] Mingming Liang et al., *Efficacy of Face Mask in Preventing Respiratory Virus Transmission: A Systematic Review and Meta-Analysis*, 36 TRAVEL MED. & INFECTIOUS DISEASE 1, 7 (2020).

[357] Hanna M. Ollila et al., *Face Masks Prevent Transmission of Respiratory Diseases: A Meta-Analysis of Randomized Controlled Trials*, MEDRXIV 1, 12 (2020), https://www.medrxiv.org/content/10.1101/2020.07.31.20166116v2.full.pdf.

	efficacy at maximum follow up (7.8% (297/3793) vs. 18.4% (704/3830); RR: 0.608). However, for 2 of the 5 papers studied the authors utilize data from face mask + other intervention arms instead of available data from face mask-only arm. These risk ratios are considerably different (0.78 and 0.88 instead of 1.10 and 0.92, respectively) and the involved groups constitute 14.3% (542/3793) and 16.4% (629/3830) of each treatment group, which would likely alter the final result.	analysis." "Despite . . . small effect sizes in the individual studies, the findings did support use of face masks."
Perski et al.[358] 2020	21 [11] (11) Authors considered 10 observational studies and 11 RCTs (only one of which found a reduction in self-reported ILIs in participants wearing face masks) and, using a Bayesian analysis, reported a "moderate likelihood of a small effect for the wearing of face masks" in reducing self-reported ILI (cumulative posterior odds=3.61), but determined that evidence was equivocal as to clinically- and laboratory-confirmed infections (cumulative posterior odds of 1.07 and 1.22, respectively).	[equivocal] RCT evidence was "equivocal on whether facemask wearing in community settings reduces the transmission of clinically- or laboratory-confirmed viral respiratory infections." "RCTs and observational studies have found an effect on self-reported symptoms, but this may be the result of reporting bias and confounding."
Wang et al.[359] 2020	15 [15] (5) Using 15 non-healthcare studies (10 observational and 5 RCTs), authors reported a slightly decreased pooled odds ratio (OR: 0.96, 95% CI 0.8–1.15) but the results were not statistically significant.	[critical] "Our review found that SMs [surgical masks] were not associated to ARI [acute respiratory illnesses] incidence, indicating that SMs may be ineffective . . . when worn by an uninfected individual in the general community. However, given the weak methodologies across studies assessed and the possibility of residual confounding, an absence of evidence cannot be simply regarded as an evidence of absence."
Xiao et al.[360] 2020	14 [14] (14) Incorporating data from 10 RCTs in non-healthcare settings, reported no statistically significant effect for the use of masks on laboratory-confirmed influenza (2.3% (29/1276) vs. 3.3% (51/1567), P=.25).	[critical] "We did not find evidence that surgical-type face masks are effective in reducing laboratory-confirmed influenza transmission, either when worn by infected persons (source control) or by persons in the general community to reduce their susceptibility."
Li et al.[361]	6 [1] (0)	[supportive]

[358] Olga Perski et al., *Face Masks to Prevent Community Transmission of Viral Respiratory Infections: A Rapid Evidence Review Using Bayesian Analysis*, QEIOS 1, 15, https://www.qeios.com/read/1SC5L4 (last visited Oct. 21, 2020).

[359] Min X. Wang et al., *Effectiveness of Surgical Face Masks in Reducing Acute Respiratory Infections in Non-Healthcare Settings: A Systematic Review and Meta-Analysis*, 7 FRONTIERS MED. 1, 20 (2020).

[360] Jingyi Xiao et al., *Nonpharmaceutical Measures for Pandemic Influenza in Nonhealthcare Settings—Personal Protective and Environmental Measures*, 26 EMERGING INFECTIOUS DISEASES 967, 972 (2020).

[361] Yanni Li et al., *Face Masks To Prevent Transmission of COVID-19: A Systematic Review and Meta-Analysis*, 49 AM. J. INFECTION CONTROL 900, 904–5 (2021).

2021	Using data from 6 COVID-19 case-control studies—5 in healthcare settings—to report a significantly-reduced risk of infection (11.4% (82/718) vs. 20.0% (202/1008); OR: 0.38). However, in the only non-HCW study considered the results were non-significant (12.8% (29/227) vs. 16.9% (102/602); OR: 0.72, 95% CI: 0.46–1.12).	"Face masks reduced the risk of COVID-19 infection by 70% for health care workers," but the "included original studies did not make . . . adjustments for possible confounding factors, such as . . . hand hygiene" and the two most heavily weighted studies involved exclusively N95 masks or primarily non-cloth masks.
Tabatabaeizadeh[362] 2020	4 [1] (0) Authors used data from 4 observational COVID-19 studies to conclude that mask-wearing is correlated with statistically significant risk ratio decrease of 0.12. However, 70.8% (n=5442) of the study's total participants (n=7688) came from a single paper where participants used N95 respirators, not facemasks.	[supportive] "[U]se of the face mask was associated significantly with a decrease [sic] risk of SARS-CoV-2 infection" but "[t]he non-randomized design of the included studies in this meta-analysis" was an "important limitation."
Coclite et al.[363] 2021	13 [13] (3) Authors used data from 3 RCTs and 10 observational papers to conduct two separate meta-analyses. Concluded that neither RCT data (11.7% (187/1598) vs. 11.2% (272/2419); RR: 0.97, P=0.85) nor any of the observational data (cross-sectional: 20.2% (1302/6438) vs. 17.2% (1714/9975); RR: 0.90, 95% CI: 0.74–1.10) (case-control: 19.9% (138/694) vs. 40.5% (327/807); RR: 0.59, 95% CI: 0.34–1.03) (prospective: 20.5% (88/429) vs. 58.4% (310/531); RR: 0.55, 95% CI: 0.11–2.75)) were statistically significant.	[supportive] "We found very low-certainty evidence that wearing a face mask is associated with a reduced risk of primary infection in RCTs as well as in observational studies." "The results… support[] the use of face masks for reducing the transmission and acquisition of respiratory viral infections in the community."
Abdullahi et al.[364] 2020	2 [3] (5) Considering data from 2 RCTs and 3 observational studies in the SARS-CoV-1 and influenza contexts, authors failed to find a statistically significant benefit of face mask use (18.7% (142/758) vs. 33.1% (480/1451); RR: 0.78, P=0.52).	[equivocal] "On the intervention on face masks, there are contested discussions…. However, WHO acknowledges that the wearing of masks by the general public has been impactful in reducing previous severe pandemics."
Nanda et al.[365] 2021	7 [7] (7) Incorporating data from 7 RCTs (all previously discussed) evaluating ILI transmission, found no significant difference in infection between mask and no-mask groups (2.8% (37/1301) vs. 3.6% (57/1592); RR: 1.00, P=0.93).	[equivocal] "The available preclinical findings limited clinical and indirect evidence suggests biological plausibility that face masks may reduce the spread of SARS-CoV-2. The available clinical trial evidence shows no significant difference in limiting transmission [of] respiratory viral illnesses, but the evidence is of poor quality."

[362] Seyed-Amer Tabatabaeizadeh, *Airborne Transmission of COVID-19 and the Role of Face Mask to Prevent It: A Systematic Review and Meta-Analysis*, 26 EUR. J. MED. RESEARCH 1, 4, 5 (2021).
[363] Daniela Coclite et al., *Face Mask Use in the Community for Reducing the Spread of COVID-19: A Systematic Review*, 7 FRONTIERS MED. 1, 8–11 (2021).
[364] Leila Abdullahi et al., *Community Interventions in Low- and Middle-Income Countries to Inform COVID-19 Control Implementation Decisions in Kenya: A Rapid Systematic Review*, 15 PLOS ONE 1, 16, 22 (2020).
[365] Akriti Nanda et al., *Efficacy of Surgical Masks or Cloth Masks in the Prevention of Viral Transmission: Systematic Review, Meta-Analysis, and Proposal for Future Trial*, 14 J. EVIDENCE-BASED MED. 97 (2021).

Table 3. Studies suggesting an association of face masks with higher rates of infection

Authors	Year	Study type (N)	Results suggestive of harm	Conclusions
Alfelali et al.[366]	2019	Cluster-randomized trial (7,687)	Unvaccinated pilgrims had higher CRI (clinical respiratory infection) rates than counterparts in the control group (13% versus 10%, P=0.03).	"[A]llocation to facemask use was not associated with reduced laboratory-confirmed viral respiratory infections or clinical respiratory infections."
MacIntyre et al.[367]	2015	Cluster-randomized trial (1607)	Rates of ILI in cloth mask intervention arm were more than 3 times higher compared to the "standard practice" control arm (2.3% (13/569) vs. 0.7% (3/458)).	Future research should examine "cloth masks, but until such research is carried out cloth masks should not be recommended." The authors "recommend that infection control guidelines be updated about cloth mask use [referring to its risks] to protect the occupational health and safety of [healthcare workers]."
Simmerman et al.[368]	2011	Cluster-randomized trial (885)	More laboratory-confirmed secondary infections among members in the hand washing plus mask group compared to the control group (23% (66/291) vs. 19% (58/302), n.s.), higher rates at the household level (35% vs. 22%) and, in a separate sub-group analysis, higher rates of ILI among those in the mask group (OR: 2.15, P=0.004) that the researchers described as "twofold in the opposite direction from the hypothesized protective effect."	Reported that "[i]nfluenza transmission was not reduced by interventions to promote hand washing and face mask use."
Larson et al.[369]	2010	Cluster-randomized trial (509 households)	Households in the hand sanitizer group included significantly more members without any reported upper respiratory symptoms compared to the hand sanitizer plus face mask group (57.6% (545/946) vs. 38.7% (363/938), P<0.01)	Did not have sufficient data to support mask wearing but nevertheless concluded that "[m]ask wearing is a promising non-pharmaceutical intervention . . ."
MacIntyre et al.[370]	2009	Cluster-randomized trial (145)	Point estimates of the primary outcome measure of ILI were higher in the surgical mask group than in the no mask group (22.3% vs. 16.0%), but the results were not statistically significant.	Authors "found that distributing masks during seasonal winter influenza outbreaks is an ineffective control measure characterized by low adherence" and stated that masks may only have efficacy "where a larger adherence may be

[366] Mohammad Alfelali et al., *Facemask Against Viral Respiratory Infections Among Hajj Pilgrims: A Challenging Cluster-Randomized Trial*, 15 PLOS ONE 1, 7 (2020).
[367] Chandini R. MacIntyre et al., *A Cluster Randomised Trial of Cloth Masks Compared with Medical Masks in Healthcare Workers*, 5 BMJ OPEN 1, 8 (2015).
[368] James M. Simmerman et al., *Findings from a Household Randomized Controlled Trial of Hand Washing and Face Masks to Reduce Influenza Transmission in Bangkok, Thailand: Household Randomized Controlled Trial of Hand Washing and Face Masks*, 5 INFLUENZA & OTHER RESPIRATORY VIRUSES 256, 256 (2011).
[369] Elaine L. Larson et al., *Impact of Non-pharmaceutical Interventions on URIs and Influenza in Crowded, Urban Households*, 125 PUB. HEALTH REP. 178, 189 (2010).
[370] Chandini R. MacIntyre et al., *Face Mask Use and Control of Respiratory Virus Transmission in Households*, 15 EMERGING INFECTIOUS DISEASES 233, 238 (2009).

				expected, such as during a severe influenza pandemic or other emerging infection."
Al-Asmary et al.[371]	2007	Nested case-control (375)	Intermittent use of face masks associated with a higher rate of acute respiratory tract infections than not wearing masks (34% (42/122) vs. 22% (4/18)).	"The common practice among pilgrims and medical personnel of using surgical facemasks to protect themselves against ARI [acute respiratory infections] should be discontinued."

[371] Saeed Al-Asmary et al., *Acute Respiratory Tract Infections Among Hajj Medical Mission Personnel, Saudi Arabia*, 11 INT'L J. INFECTIOUS DISEASE 268, 271 (2007).

Exhibit 8

International Journal of
Environmental Research and Public Health

MDPI

Review

Is a Mask That Covers the Mouth and Nose Free from Undesirable Side Effects in Everyday Use and Free of Potential Hazards?

Kai Kisielinski [1], Paul Giboni [2], Andreas Prescher [3], Bernd Klosterhalfen [4], David Graessel [5], Stefan Funken [6], Oliver Kempski [7] and Oliver Hirsch [8,*]

1 Private Practice, 40212 Düsseldorf, Germany; kaikisielinski@yahoo.de
2 Private Practice, 22763 Hamburg, Germany; pgiboni@gmx.de
3 Institute of Molecular and Cellular Anatomy (MOCA), Wendlingweg 2, 52074 Aachen, Germany; aprescher@ukaachen.de
4 Institute of Pathology, Dueren Hospital, Roonstrasse 30, 52351 Dueren, Germany; bernd.klosterhalfen@web.de
5 Institute of Neuroscience and Medicine, Forschungszentrum Jülich, 52425 Jülich, Germany; d.graessel@fz-juelich.de
6 Private Practice, 47803 Krefeld, Germany; dr_funken@colita.net
7 Institute of Neurosurgical Pathophysiology, University Medical Centre of the Johannes Gutenberg University of Mainz Langenbeckstr. 1, 55131 Mainz, Germany; oliver.kempski@unimedizin-mainz.de
8 Department of Psychology, FOM University of Applied Sciences, 57078 Siegen, Germany
* Correspondence: oliver.hirsch@fom.de

Citation: Kisielinski, K.; Giboni, P.; Prescher, A.; Klosterhalfen, B.; Graessel, D.; Funken, S.; Kempski, O.; Hirsch, O. Is a Mask That Covers the Mouth and Nose Free from Undesirable Side Effects in Everyday Use and Free of Potential Hazards?. *Int. J. Environ. Res. Public Health* **2021**, *18*, 4344. https://doi.org/10.3390/ijerph18084344

Academic Editor: Paul B. Tchounwou

Received: 20 March 2021
Accepted: 16 April 2021
Published: 20 April 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Abstract: Many countries introduced the requirement to wear masks in public spaces for containing SARS-CoV-2 making it commonplace in 2020. Up until now, there has been no comprehensive investigation as to the adverse health effects masks can cause. The aim was to find, test, evaluate and compile scientifically proven related side effects of wearing masks. For a quantitative evaluation, 44 mostly experimental studies were referenced, and for a substantive evaluation, 65 publications were found. The literature revealed relevant adverse effects of masks in numerous disciplines. In this paper, we refer to the psychological and physical deterioration as well as multiple symptoms described because of their consistent, recurrent and uniform presentation from different disciplines as a Mask-Induced Exhaustion Syndrome (MIES). We objectified evaluation evidenced changes in respiratory physiology of mask wearers with significant correlation of O_2 drop and fatigue ($p < 0.05$), a clustered co-occurrence of respiratory impairment and O_2 drop (67%), N95 mask and CO_2 rise (82%), N95 mask and O_2 drop (72%), N95 mask and headache (60%), respiratory impairment and temperature rise (88%), but also temperature rise and moisture (100%) under the masks. Extended mask-wearing by the general population could lead to relevant effects and consequences in many medical fields.

Keywords: personal protective equipment; masks; N95 face mask; surgical mask; risk; adverse effects; long-term adverse effects; contraindications; health risk assessment; hypercapnia; hypoxia; headache; dyspnea; physical exertion; MIES syndrome

1. Introduction

At the beginning of the spread of the novel pathogen SARS-CoV-2, it was necessary to make far-reaching decisions even without available explicit scientific data. The initial assumption was that the pandemic emergency measures were set in place to reduce the acute threat of the public health system effectively and swiftly.

In April 2020, the World Health Organization (WHO) recommended the use of masks only for symptomatic, ill individuals and health care workers and did not recommend its widespread use.

In June 2020, they changed this recommendation to endorse the general use of masks in, e.g., crowded places [1,2]. In a meta-analysis study commissioned by the WHO (evidence level Ia), no clear, scientifically graspable benefit of moderate or strong evidence was derived from wearing masks [3].

While maintaining a distance of at least one meter showed moderate evidence with regard to the spreading of SARS-CoV-2, only weak evidence at best could be found for masks alone in everyday use (non-medical setting) [3]. Another meta-analysis conducted in the same year confirmed the weak scientific evidence for masks [4].

Accordingly, the WHO did not recommend general or uncritical use of masks for the general population and expanded its risk and hazard list within just two months. While the April 2020 guideline highlighted the dangers of self-contamination, possible breathing difficulties and false sense of security, the June 2020 guideline found additional potential adverse effects such as headache, development of facial skin lesions, irritant dermatitis, acne or increased risk of contamination in public spaces due to improper mask disposal [1,2].

However, under pressure from increasing absolute numbers of positive SARS-CoV-2 tests, many prescribers further extended mask-wearing according to certain times and situations, always justified by the desire to limit the spread of the virus [5]. The media, numerous institutions and most of the population supported this approach.

Among the medical profession and scientists, the users and observers of medical devices, there have been simultaneous calls for a more nuanced approach [6–8]. While there has been a controversial scientific discussion worldwide about the benefits and risks of masks in public spaces, they became the new social appearance in everyday life in many countries at the same time.

Although there seems to be a consensus among the decision makers who have introduced mandatory masks that medical exemptions are warranted, it is ultimately the responsibility of individual clinicians to weigh up when to recommend exemption from mandatory masks. Physicians are in a conflict of interest concerning this matter. On the one hand, doctors have a leading role in supporting the authorities in the fight against a pandemic. On the other hand, doctors must, in accordance with the medical ethos, protect the interests, welfare and rights of their patient's third parties with the necessary care and in accordance with the recognized state of medical knowledge [9–11].

A careful risk–benefit analysis is becoming increasingly relevant for patients and their practitioners regarding the potential long-term effects of masks. The lack of knowledge of legal legitimacy on the one hand and of the medical scientific facts on the other is a reason for uncertainty among clinically active colleagues.

The aim of this paper is to provide a first, rapid, scientific presentation of the risks of general mandatory mask use by focusing on the possible adverse medical effects of masks, especially in certain diagnostic, patient and user groups.

2. Materials and Methods

The objective was to search for documented adverse effects and risks of different types of mouth–nose-covering masks. Of interest here were, on the one hand, readymade and self-manufactured fabric masks, including so-called community masks and, on the other hand medical, surgical and N95 masks (FFP2 masks).

Our approach of limiting the focus to negative effects seems surprising at first glance. However, such an approach helps toprovide us with more information. This methodology is in line with the strategy of Villalonga-Olives and Kawachi, who also conducted a review exclusively on the negative effects [12].

For an analysis of the literature, we defined the risk of mouth–nose protection as the description of symptoms or the negative effects of masks. Reviews and expert presentations from which no measurable values could be extracted, but which clearly present the research situation and describe negative effects, also fulfill this criterion.

Additionally, we defined the quantifiable, negative effect of masks as the presentation of a measured, statistically significant change in a physiological parameter in a pathological direction ($p < 0.05$), a statistically significant detection of symptoms ($p < 0.05$) or the occurrence of symptoms in at least 50% of those examined in a sample ($n \geq 50\%$).

Up to and including 31 October 2020, we conducted a database search in PubMed/MEDLINE on scientific studies and publications on adverse effects and risks of different types of mouth–nose-covering masks according to the criteria mentioned above (see Figure 1: Review flowchart). Terms searched were "face masks", "surgical mask" and "N95" in combination with the terms "risk" and "adverse effects" as well as "side effects". The selection criteria of the papers were based on our above definition of risk and adverse effect of masks. Mainly English- and German-language publications of evidence levels I to III according to the recommendations of the Agency for Healthcare Research and Quality (AHQR) that were not older than 20 years at the time of the review were considered. The evaluation also excluded level IV evidence, such as case reports and irrelevant letters to the editor that exclusively reflect opinions without scientific evidence.

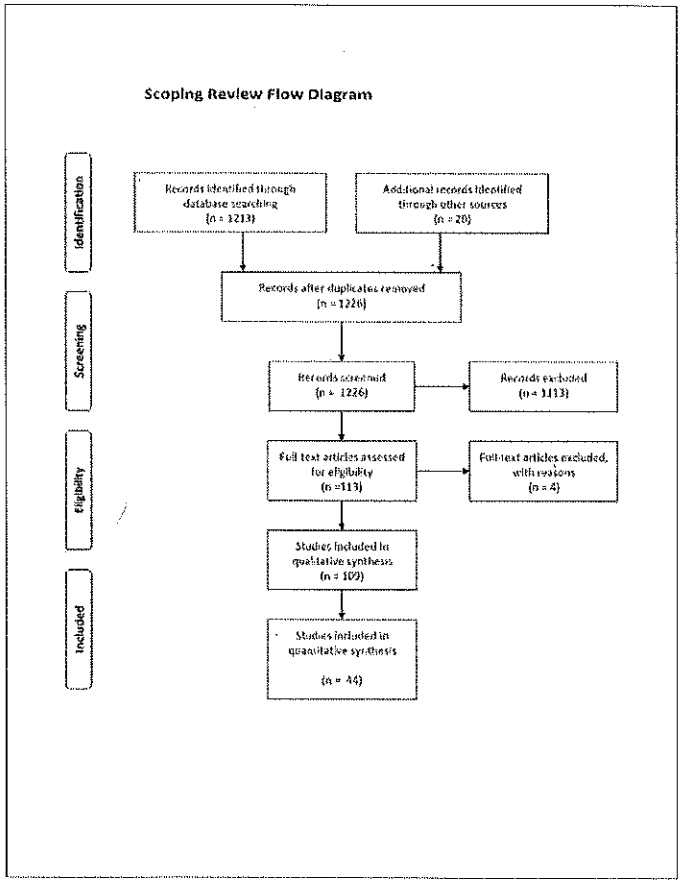

Figure 1. Scoping review flow diagram according to the PRISMA scheme.

After excluding 1113 papers that were irrelevant to the research question and did not meet the criteria mentioned (quantifiable, negative effects of masks, description of symptoms or the negative effects of masks), a total of 109 relevant publications were found for evaluation in the context of our scoping review (see Figure 1: Flow chart).

Sixty-five relevant publications concerning masks were considered being within the scope of the content-related evaluation. These included 14 reviews and 2 meta-analyses from the primary research. For the quantitative evaluation, 44 presentations of nega-

tive effects from the years 2004 to 2020 were eligible. Thirty-one of these studies were experimental (70%), and 13 studies were data collection studies in the sense of simple observational studies, especially in the dermatological field (30%). The observed study parameters and significant results from these 44 publications ($p < 0.05$ or $n \geq 50\%$) were compiled in an overall display (Figure 2). Based on this data, a correlation analysis of the observed mask effects was performed. This included a correlation calculation of the recorded symptoms and physiological changes (for nominally scaled, dichotomous variables according to Fisher using R, R Foundation for Statistical Computing, Vienna, Austria, version 4.0.2).

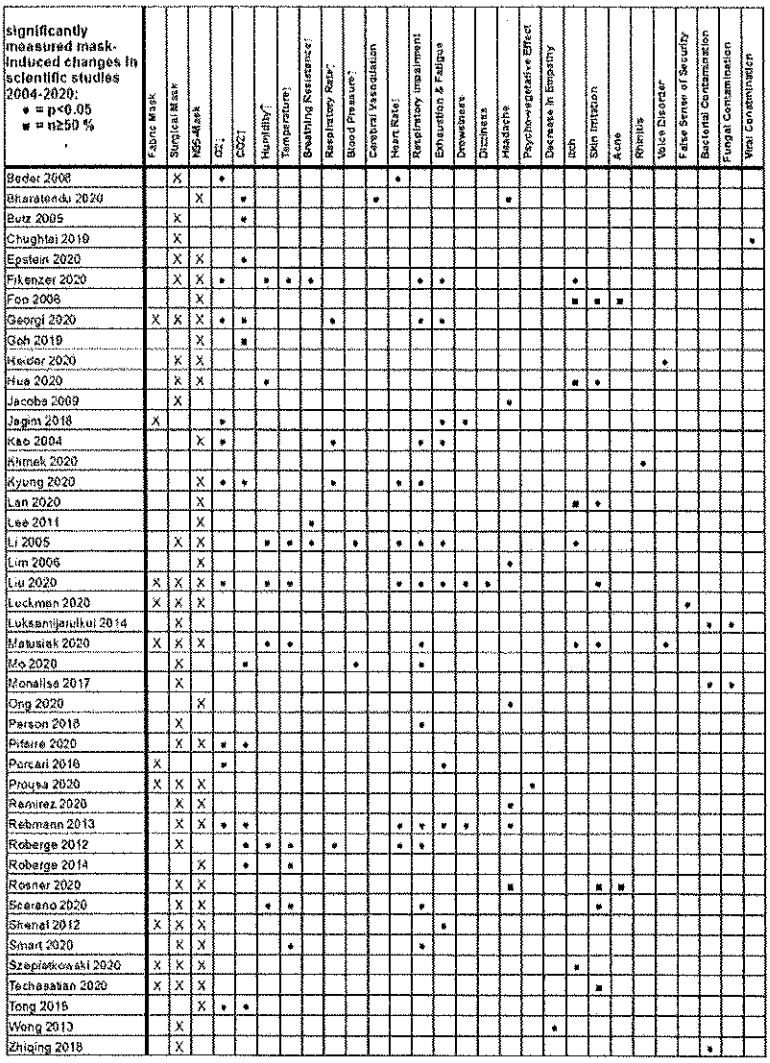

Figure 2. Overview including all 44 considered studies with quantified, significant adverse effects of masks (black dots and black rectangles). Not all studies examined each mentioned parameter, as focused or subject-related questions were often in the foreground. Gray fields correspond to a lack of coverage in the primary studies, white fields represent measured effects. We found an often combination of significant chemical, physical, physiological parameters and complaints. Drowsiness summarizes the symptom for any qualitative neurological deficits described in the scientific literature examined.

In addition, another 64 publications with a neighboring range of topics were consulted in connection with the mask effects we found. These included declarations, guidelines

and legal principles. In order to expand the amount of data for the discussion, we proceeded according to the "snowball principle" by locating citations of selected papers in the bibliographies and including them where appropriate.

Since the findings from the topics presented for discussion were to an unexpected degree subject-related, we decided to divide the results according to the fields of medicine. Of course, there are overlaps between the respective fields, which we point out in detail.

3. Results

A total of 65 scientific papers on masks qualified for a purely content-based evaluation. These included 14 reviews and two meta-analyses.

Of the mathematically evaluable, groundbreaking 44 papers with significant negative mask effects ($p < 0.05$ or $n \geq 50\%$), 22 were published in 2020 (50%), and 22 were published before the COVID-19 pandemic. Of these 44 publications, 31 (70%) were of experimental nature, and the remainder were observational studies (30%). Most of the publications in question were English (98%). Thirty papers referred to surgical masks (68%), 30 publications related to N95 masks (68%), and only 10 studies pertained to fabric masks (23%).

Despite the differences between the primary studies, we were able to demonstrate a statistically significant correlation in the quantitative analysis between the negative side effects of blood-oxygen depletion and fatigue in mask wearers with $p = 0.0454$.

In addition, we found a mathematically grouped common appearance of statistically significant confirmed effects of masks in the primary studies ($p < 0.05$ and $n \geq 50\%$) as shown in Figure 2. In nine of the 11 scientific papers (82%), we found a combined onset of N95 respiratory protection and carbon dioxide rise when wearing a mask. We found a similar result for the decrease in oxygen saturation and respiratory impairment with synchronous evidence in six of the nine relevant studies (67%). N95 masks were associated with headaches in six of the 10 studies (60%). For oxygen deprivation under N95 respiratory protectors, we found a common occurrence in eight of 11 primary studies (72%). Skin temperature rise under masks was associated with fatigue in 50% (three out of six primary studies). The dual occurrence of the physical parameter temperature rise and respiratory impairment was found in seven of the eight studies (88%). A combined occurrence of the physical parameters temperature rise and humidity/moisture under the mask was found in 100% within six of six studies, with significant readings of these parameters (Figure 2).

The literature review confirms that relevant, undesired medical, organ and organ system-related phenomena accompanied by wearing masks occur in the fields of internal medicine (at least 11 publications, Section 3.2). The list covers neurology (seven publications, Section 3.3), psychology (more than 10 publications, Section 3.4), psychiatry (three publications, Section 3.5), gynecology (three publications, Section 3.6), dermatology (at least 10 publications, Section 3.7), ENT medicine (four publications, Section 3.8), dentistry (one publication, Section 3.8), sports medicine (four publications, Section 3.9), sociology (more than five publications, Section 3.10), occupational medicine (more than 14 publications, Section 3.11), microbiology (at least four publications, Section 3.12), epidemiology (more than 16 publications, Section 3.13), and pediatrics (four publications, Section 3.14) as well as environmental medicine (four publications, Section 3.15).

We will present the general physiological effects as a basis for all disciplines. This will be followed by a description of the results from the different medical fields of expertise and closing off with pediatrics the final paragraph.

3.1. General Physiological and Pathophysiological Effects for the Wearer

As early as 2005, an experimental dissertation (randomized crossover study) demonstrated that wearing surgical masks in healthy medical personnel (15 subjects, 18–40 years old) leads to measurable physical effects with elevated transcutaneous carbon dioxide values after 30 min [13]. The role of dead space volume and CO_2 retention as a cause of the significant change ($p < 0.05$) in blood gases on the way to hypercapnia, which was still

within the limits, was discussed in this article. Masks expand the natural dead space (nose, throat, trachea, bronchi) outwards and beyond the mouth and nose.

An experimental increase in the dead space volume during breathing increases carbon dioxide (CO_2) retention at rest and under exertion and correspondingly the carbon dioxide partial pressure pCO_2 in the blood ($p < 0.05$) [14].

As well as addressing the increased rebreathing of carbon dioxide (CO_2) due to the dead space, scientists also debate the influence of the increased breathing resistance when using masks [15–17].

According to the scientific data, mask wearers as a whole show a striking frequency of typical, measurable, physiological changes associated with masks.

In a recent intervention study conducted on eight subjects, measurements of the gas content for oxygen (measured in O_2 Vol%) and carbon dioxide (measured in CO_2 ppm) in the air under a mask showed a lower oxygen availability even at rest than without a mask. A Multi-Rae gas analyzer was used for the measurements (RaeSystems®) (Sunnyvale, California CA, United States). At the time of the study, the device was the most advanced portable multivariant real-time gas analyzer. It is also used in rescue medicine and operational emergencies. The absolute concentration of oxygen (O_2 Vol%) in the air under the masks was significantly lower (minus 12.4 Vol% O_2 in absolute terms, statistically significant with $p < 0.001$) at 18.3% compared to 20.9% room air concentration. Simultaneously, a health-critical value of carbon dioxide concentration (CO_2 Vol%) increased by a factor of 30 compared to normal room air was measured (ppm with mask versus 464 ppm without mask, statistically significant with $p < 0.001$) [18].

These phenomena are responsible for a statistically significant increase in carbon dioxide (CO_2) blood content in mask wearers [19,20], on the one hand, measured transcutaneously via an increased $PtcCO_2$ value [15,17,19,21,22], on the other hand, via end-expiratory partial pressure of carbon dioxide ($PETCO_2$) [23,24] or, respectively, the arterial partial pressure of carbon dioxide ($PaCO_2$) [25].

In addition to the increase in the wearer's blood carbon dioxide (CO_2) levels ($p < 0.05$) [13,15,17,19,21–28], another consequence of masks that has often been experimentally proven is a statistically significant drop in blood oxygen saturation (SpO_2) ($p < 0.05$) [18,19,21,23,29–34]. A drop in blood oxygen partial pressure (PaO_2) with the effect of an accompanying increase in heart rate ($p < 0.05$) [15,23,29,30,34] as well as an increase in respiratory rate ($p < 0.05$) [15,21,23,35,36] have been proven.

A statistically significant measurable increase in pulse rate ($p < 0.05$) and decrease in oxygen saturation SpO_2 after the first ($p < 0.01$) and second hour ($p < 0.0001$) under a disposable mask (surgical mask) were reported by researchers in a mask intervention study they conducted on 53 employed neurosurgeons [30].

In another experimental study (comparative study), surgical and N95 masks caused a significant increase in heart rate ($p < 0.01$) as well as a corresponding feeling of exhaustion ($p < 0.05$). These symptoms were accompanied by a sensation of heat ($p < 0.0001$) and itching ($p < 0.01$) due to moisture penetration of the masks ($p < 0.0001$) in 10 healthy volunteers of both sexes after only 90 min of physical activity [35]. Moisture penetration was determined via sensors by evaluating logs (SCXI-1461, National Instruments, Austin, TX, USA).

These phenomena were reproduced in another experiment on 20 healthy subjects wearing surgical masks. The masked subjects showed statistically significant increases in heart rate ($p < 0.001$) and respiratory rate ($p < 0.02$) accompanied by a significant measurable increase in transcutaneous carbon dioxide $PtcCO_2$ ($p < 0.0006$). They also complained of breathing difficulties during the exercise [15].

The increased rebreathing of carbon dioxide (CO_2) from the enlarged dead space volume in mask wearers can reflectively trigger increased respiratory activity with increased muscular work as well as the resulting additional oxygen demand and oxygen consumption [17]. This is a reaction to pathological changes in the sense of an adaptation effect. A mask-induced drop in blood oxygen saturation value (SpO_2) [30] or the blood

oxygen partial pressure (PaO_2) [34] can in turn additionally intensify subjective chest complaints [25,34].

The documented mask-induced changes in blood gases towards hypercapnia (increased carbon dioxide/CO_2 blood levels) and hypoxia (decreased oxygen/O_2 blood levels) may result in additional nonphysical effects such as confusion, decreased thinking ability and disorientation [23,36–39], including overall impaired cognitive abilities and decrease in psychomotoric abilities [19,32,38–41]. This highlights the importance of changes in blood gas parameters (O_2 and CO_2) as a cause of clinically relevant psychological and neurological effects. The above parameters and effects (oxygen saturation, carbon dioxide content, cognitive abilities) were measured in a study on saturation sensors (Semi-Tec AG, Therwil, Switzerland), using a Borg Rating Scale, Frank Scale, Roberge Respirator Comfort Scale and Roberge Subjective Symptoms-during-Work Scale, as well as with a Likert scale [19]. In the other main study, conventional ECG, capnography and symptom questionnaires were used in measuring carbon dioxide levels, pulse and cognitive abilities [23]. Other physiological data collection was done with pulse oximeters (Allegiance, MCGaw, USA), subjective complaints were assessed with a 5-point Likert scale and motoric speed was recorded with linear-position transducers (Tendo-Fitrodyne, Sport Machins, Trencin, Slovakia) [32]. Some researchers used standardized, anonymized questionnaires to collect data on subjective complaints associated with masks [37].

In an experimental setting with different mask types (community, surgical, N95) a significant increase in heart rate ($p < 0.04$), a decrease in oxygen saturation SpO_2 ($p < 0.05$) with an increase in skin temperature under the mask (face) and difficulty of breathing ($p < 0.002$) were recorded in 12 healthy young subjects (students). In addition, the investigators observed dizziness ($p < 0.03$), listlessness ($p < 0.05$), impaired thinking ($p < 0.03$) and concentration problems ($p < 0.02$), which were also statistically significant when wearing masks [29].

According to other researchers and their publications, masks also interfere with temperature regulation, impair the field of vision and of non-verbal and verbal communication [15,17,19,36,37,42–45].

The above-mentioned measurable and qualitative physiological effects of masks can have implications in various areas of expertise in medicine.

It is known from pathology that not only supra-threshold stimuli exceeding normal limits have disease-relevant consequences. Subthreshold stimuli are also capable of causing pathological changes if the exposure time is long enough. Examples occur from the slightest air pollution by hydrogen sulfide resulting in respiratory problems (throat irritation, coughing, reduced absorption of oxygen) and neurological diseases (headaches, dizziness) [46]. Furthermore, subthreshold but prolonged exposure to nitrogen oxides and particulate matter is associated with an increased risk of asthma, hospitalization and higher overall mortality [47,48]. Low concentrations of pesticides are also associated with disease-relevant consequences for humans such as mutations, development of cancer and neurological disorders [49]. Likewise, the chronic subthreshold intake of arsenic is associated with an increased risk of cancer [50], subthreshold intake of cadmium with the promotion of heart failure [51], subthreshold intake of lead is associated with hypertension, renal metabolic disorders and cognitive impairment [52] or subthreshold intake of mercury with immune deficiency and neurological disorders [53]. Subliminal UV radiation exposure over long periods is also known to cause mutation-promoting carcinogenic effects (especially white skin cancer) [54].

The mask-induced adverse changes are relatively minor at first glance, but repeated exposure over longer periods in accordance with the above-mentioned pathogenetic principle is relevant. Long-term disease-relevant consequences of masks are to be expected. Insofar, the statistically significant results found in the studies with mathematically tangible differences between mask wearers and people without masks are clinically relevant. They give an indication that with correspondingly repeated and prolonged exposure to physical, chemical, biological, physiological and psychological conditions, some of which are

subliminal, but which are significantly shifted towards pathological areas, health-reducing changes and clinical pictures can develop such as high blood pressure and arteriosclerosis, including coronary heart disease (metabolic syndrome) as well as neurological diseases. For small increases in carbon dioxide in the inhaled air, this disease-promoting effect has been proven with the creation of headaches, irritation of the respiratory tract up to asthma as well as an increase in blood pressure and heart rate with vascular damage and, finally, neuropathological and cardiovascular consequences [38]. Even slightly but persistently increased heart rates encourage oxidative stress with endothelial dysfunction, via increased inflammatory messengers, and finally, the stimulation of arteriosclerosis of the blood vessels has been proven [55]. A similar effect with the stimulation of high blood pressure, cardiac dysfunction and damage to blood vessels supplying the brain is suggested for slightly increased breathing rates over long periods [56,57]. Masks are responsible for the aforementioned physiological changes with rises in inhaled carbon dioxide [18–28], small sustained increases in heart rate [15,23,29,30,35] and mild but sustained increases in respiratory rates [15,21,23,34,36].

For a better understanding of the side effects and dangers of masks presented in this literature review, it is possible to refer to well-known principles of respiratory physiology (Figure 3).

The average dead space volume during breathing in adults is approximately 150–180 mL and is significantly increased when wearing a mask covering the mouth and nose [58]. With an N95 mask, for example, the dead space volume of approximately 98–168 mL was determined in an experimental study [59]. This corresponds to a mask-related dead space increase of approximately 65 to 112% for adults and, thus, almost a doubling. At a respiratory rate of 12 per minute, the pendulum volume respiration with such a mask would, thus, be at least 2.9–3.8 L per minute. Therefore, the dead space amassed by the mask causes a relative reduction in the gas exchange volume available to the lungs per breath by 37% [60]. This largely explains the impairment of respiratory physiology reported in our work and the resulting side effects of all types of masks in everyday use in healthy and sick people (increase in respiratory rate, increase in heart rate, decrease in oxygen saturation, increase in carbon dioxide partial pressure, fatigue, headaches, dizziness, impaired thinking, etc.) [36,58].

In addition to the effect of increased dead space volume breathing, however, mask-related breathing resistance is also of exceptional importance (Figure 3) [23,36].

Experiments show an increase in airway resistance by a remarkable 126% on inhalation and 122% on exhalation with an N95 mask [60]. Experimental studies have also shown that moisturization of the mask (N95) increases the breathing resistance by a further 3% [61] and can, thus, increase the airway resistance up to 2.3 times the normal value.

This clearly shows the importance of the airway resistance of a mask. Here, the mask acts as a disturbance factor in breathing and makes the observed compensatory reactions with an increase in breathing frequency and simultaneous feeling of breathlessness plausible (increased work of the respiratory muscles). This extra strain due to the amplified work of breathing against bigger resistance caused by the masks also leads to intensified exhaustion with a rise in heart rate and increased CO_2 production. Fittingly, in our review of the studies on side effects of masks (Figure 2), we also found a percentage clustering of significant respiratory impairment and a significant drop in oxygen saturation (in about 75% of all study results).

In the evaluation of the primary papers, we also determined a statically significant correlation of the drop in oxygen saturation (SpO_2) and fatigue with a common occurrence in 58% of the mask use studies with significant results (Figure 2, $p < 0.05$).

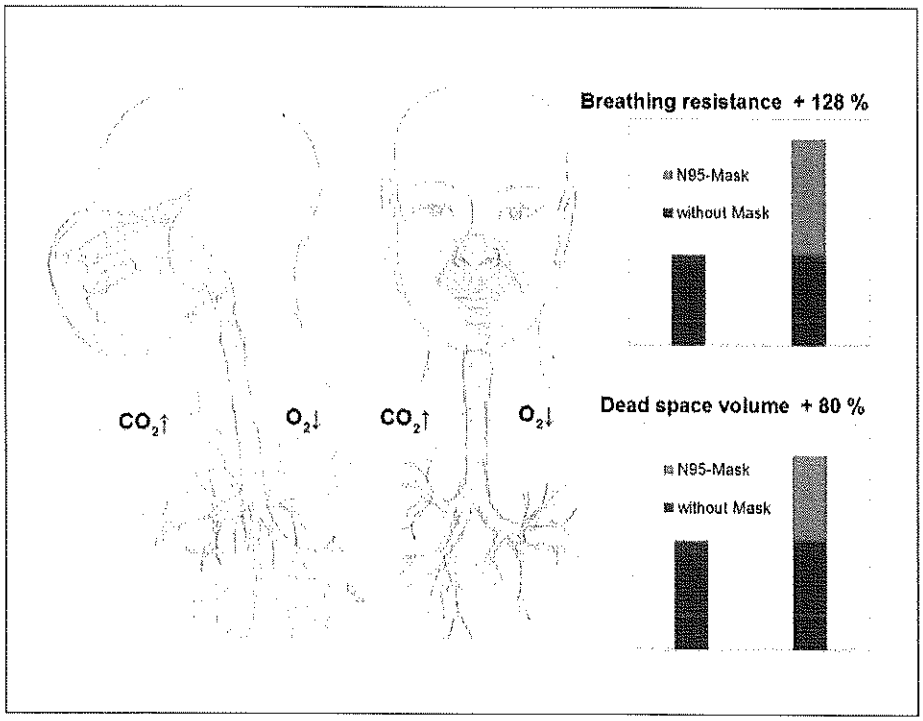

Figure 3. Pathophysiology of the mask (important physical and chemical effects): Illustration of the breathing resistance* and of the dead space volume of an N95 mask in an adult. When breathing, there is an overall significantly reduced possible gas exchange volume of the lungs of minus 37% caused by the mask (Lee 2011) [60] according to a decrease in breathing depth and volume due to the greater breathing resistance of plus128%* (exertion when inhaling greater than when exhaling) and due to the increased dead space volume of plus80%**, which does not participate directly in the gas exchange and is being only partially mixed with the environment. (* = averaged inspiration and expiration according to Lee 2011 [60] including moisture penetration according to Roberge 2010 [61], ** = averaged values according to Xu 2015 [59]).

3.2. Internistic Side Effects and Dangers

As early as 2012, an experiment showed that walking in the 20 masked subjects compared to the identical activity without masks significantly increased heart rates (average +9.4 beats per minute, $p < 0.001$) and breathing rates ($p < 0.02$). These physiological changes were accompanied by transcutaneous significantly measurable increased transcutaneous carbon dioxide ($PtcCO_2$) levels ($p < 0.0006$) as well as respiratory difficulties in the mask wearers compared to the control group [15].

In a recent experimental comparative study from 2020, 12 healthy volunteers under surgical masks as well as under N95 masks experienced measurable impairments in the measured lung function parameters as well as cardiopulmonary capacity (lower maximum blood lactate response) during moderate to heavy physical exertion compared to exertion without masks ($p < 0.001$) [31]. The mask-induced increased airway resistance led to increased respiratory work with increased oxygen consumption and demand, both of the respiratory muscles and the heart. Breathing was significantly impeded ($p < 0.001$) and participants reported mild pain. The scientists concluded from their results that the cardiac compensation of the pulmonary, mask-induced restrictions, which still functioned in healthy people, was probably no longer possible in patients with reduced cardiac output [31].

In another recent study, researchers tested fabric masks (community masks), surgical masks and FFP2/N95 masks in 26 healthy people during exercise on a cycle ergometer. All

masks also showed a measurable carbon dioxide (CO_2) retention ($PtcCO_2$) (statistically significant with $p < 0.001$) and, for N95 masks, a decrease in the oxygen saturation value SpO_2 (statistically significant at 75 and 100 W with $p < 0.02$ and $p < 0.005$, respectively). The clinical relevance of these changes was shown in an increase in breathing frequency with fabric masks ($p < 0.04$) as well as in the occurrence of the previously described mask-specific complaints such as a feeling of heat, shortness of breath and headaches. The stress perception was recorded on a Borg scale from 1 to 20. During physical exertion under an N95 mask, the group with masks showed a significant increase in the feeling of exhaustion compared to the group without with 14.6 versus 11.9 on the scale of 20. During the exposure, 14 of the 24 subjects wearing masks complained of shortness of breath (58%), four of headaches and two of a feeling of heat. Most of the complaints concerned FFP2 masks (72%) [21].

The aforementioned physiological and subjective physical effects of masks on healthy people at rest and under exertion [21,31] give an indication of the effect of masks on sick and elderly people even without exertion.

In an observational study of ten 20 to 50 year-old nurses wearing N95 masks during their shift work, side effects such as breathing difficulties ("I can't breathe"), feelings of exhaustion, headache ($p < 0.001$), drowsiness ($p < 0.001$) and a decrease in oxygen saturation SpO_2 ($p < 0.05$) as well as an increase in heart rate ($p < 0.001$) were statistically significant in association with an increase in obesity (BMI) [19]. The occurrence of symptoms under masks was also associated with older age (statistically significant correlation of fatigue and drowsiness with $p < 0.01$ each, nausea with $p < 0.05$, an increase in blood pressure with $p < 0.01$, headache with $p < 0.05$, breathing difficulties with $p < 0.001$) [19].

In an intervention study involving 97 patients with advanced chronic obstructive pulmonary disease (COPD) the respiratory rate, oxygen saturation and exhaled carbon dioxide equivalents (capnometry) changed unfavorably and significantly after the use of N95 masks (FFP2 equivalent) with an initial 10-minute rest and subsequent 6-minute walking. Seven patients discontinued the experiment due to serious complaints with a decrease in the oxygen saturation value SpO_2 and a pathological carbon dioxide (CO_2) retention as well as increased end-expiratory partial pressure of carbon dioxide ($PETCO_2$) [23]. In two patients, the $PETCO_2$ exceeded the normal limits and reached values of >50 mmHg. An FEV1 < 30% and a modified Medical Research Council (mMRC) Dyspnea Scale Score of $\geq$3, both indicators of advanced COPD, correlated with mask intolerance overall in this study. The most common symptom under mask was breathlessness at 86%. In the dropouts of the study, dizziness (57%) and headaches were also often recorded. In the mask-tolerant COPD patients, significant increases in heart rate, respiratory rate and end-expiratory carbon dioxide partial pressure $PETCO_2$ could be objectified even at rest, after only 10 min of mask-wearing ($p < 0.001$), accompanied by a decrease in oxygen saturation SpO_2 ($p < 0.001$) [23]. The results of this study with an evidence level IIa are indicative for COPD mask wearers.

In another retrospective comparative study on COPD and surgical masks, examiners were able to demonstrate statistically an increase in arterial partial pressure of carbon dioxide ($PaCO_2$) of approximately +8 mmHg ($p < 0.005$) and a concomitant mask-related increase in systolic blood pressure of +11 mmHg ($p < 0.02$) [25]. This increase is relevant in hypertensive patients, but also in healthy people with borderline blood pressure values as pathological value range triggered by mask-wearing can be induced.

In 39 hemodialysis patients with end-stage renal disease, a type N95 mask (FFP2 equivalent) caused a significant drop in blood oxygen partial pressure (PaO_2) in 70% of patients at rest (on hemodialysis) within only 4 h ($p = 0.006$). Despite a compensatory increased respiratory rate ($p < 0.001$), malaise with chest pain occurred ($p < 0.001$) and even resulted in hypoxemia (drop in oxygen below the normal limit) in 19% of the subjects [34]. The researchers concluded from their findings that elderly or patients with reduced cardiopulmonary function have a higher risk of developing a severe respiratory failure while wearing a mask [34].

In a review paper on the risks and benefits of masks worn during the COVID-19 crisis, other authors provide an equally critical assessment of mandatory mask use for patients with pneumonia, both with and without COVID-19 pneumonia disease [16].

3.3. Neurological Side Effects and Dangers

In a scientific evaluation of syncope in the operating theatre, 36 of 77 affected persons (47%) were associated with wearing a mask [62]. However, other factors could not be ruled out as contributory causes.

In their level III evidence review, neurologists from Israel, the UK and the USA state that a mask is unsuitable for epileptics because it can trigger hyperventilation [63]. The use of a mask significantly increases the respiratory rate by about plus 15 to 20% [15,21,23,34,64]. However, an increase in breathing frequency leading to hyperventilation is known to be used for provocation in the diagnosis of epilepsy and causes seizure-equivalent EEG changes in 80% of patients with generalized epilepsy and in up to 28% of focal epileptics [65].

Physicians from New York studied the effects of wearing masks of the surgical-type mask and N95 among medical personnel in a sample of 343 participants (surveyed using standardized, anonymized questionnaires). Wearing the masks caused detectable physical adverse effects such as impaired cognition (24% of wearers) and headaches in 71.4% of the participants. Of these, 28% persisted and required medication. Headache occurred in 15.2% under 1 h of wear, in 30.6% after 1 h of wear and in 29.7% after 3 h of wear. Thus, the effect intensified with increasing wearing time [37].

Confusion, disorientation and even drowsiness (Likert scale questionnaire) and reduced motoric abilities (measured with a linear position transducer) with reduced reactivity and overall impaired performance (measured with the Roberge Subjective Symptoms-during-Work Scale) as a result of mask use have also been documented in other studies [19,23,29,32,36,37].

The scientists explain these neurological impairments with a mask-induced latent drop in blood gas oxygen levels O_2 (towards hypoxia) or a latent increase in blood gas carbon dioxide levels CO_2 (towards hypercapnia) [36]. In view of the scientific data, this connection also appears to be indisputable [38–41].

In a mask experiment from 2020, significant impaired thinking ($p < 0.03$) and impaired concentration ($p < 0.02$) were found for all mask types used (fabric, surgical and N95 masks) after only 100 min of wearing the mask [29]. The thought disorders correlated significantly with a drop in oxygen saturation ($p < 0.001$) during mask use.

Initial headaches ($p < 0.05$) were experienced by up to 82% of 158, 21–35 year-old mask wearers in another study of N95 respiratory protection with one third (34%) experiencing headaches up to four times daily. Participants wore the mask for 18.3 days over a 30-day period with a mean of 5.9 h per day [66].

Significantly increased headache ($p < 0.05$) could be observed not only for N95 but also for surgical masks in participants of another observational study of health care workers [67].

In another study, the researchers classified 306 users with an average age of 43 years and wearing different types of masks, of whom 51% had an initial headache as a specific symptom related exclusively to increased surgical and N95 mask use (1 to 4 h, $p = 0.008$) [68].

Researchers from Singapore were able to demonstrate in a trial involving 154 healthy N95 health service mask wearers that a significant increase in mask-induced blood carbon dioxide levels (measured by end-expiratory partial pressure of carbon dioxide $PETCO_2$) and a measurably greater vasodilatation with an increase in cerebral artery flow in the cerebri media resulted. This was associated with headaches in the trial group ($p < 0.001$) [27].

According to the researchers, the aforementioned changes also contribute to headaches during the prolonged use of masks with a shift towards hypoxia and hypercapnia. Furthermore, stress and mechanical factors such as the irritation of cervical nerves in the neck and head area caused by the tight mask straps pressuring the nerve strands also contribute to headaches [66].

In the analysis of the primary studies, we were able to detect an association between the N95 mask and headaches. In six out of 10 studies, the significant headache appeared in conjunction with the N95 mask (60% of all studies, Figure 2).

3.4. Psychological Side Effects and Dangers

According to an experimental study, wearing surgical masks and N95 masks can also lead to a reduced quality of life owing to reduced cardiopulmonary capacity [31]. Masks, along with causing physiological changes and discomfort with progressive length of use, can also lead to significant discomfort ($p < 0.03$ to $p < 0.0001$) and a feeling of exhaustion ($p < 0.05$ to 0.0001) [69].

Besides the shift in blood gases towards hypercapnia (increase in CO_2) and hypoxia (decrease in O_2), detailed under general physiological effects (Section 3.1), masks also restrict the cognitive abilities of the individual (measured using a Likert scale survey) accompanied by a decline in psycho-motoric abilities and consequently a reduced responsiveness (measured using a linear position transducer) as well as an overall reduced performance capability (measured with the Roberge Subjective Symptoms-during-Work Scale) [29,32,38,39,41].

The mask also causes an impaired field of vision (especially affecting the ground and obstacles on the ground) and also presents an inhibition to habitual actions such as eating, drinking, touching, scratching and cleaning the otherwise uncovered part of the face, which is consciously and subconsciously perceived as a permanent disturbance, obstruction and restriction [36]. Wearing masks, thus, entails a feeling of deprivation of freedom and loss of autonomy and self-determination, which can lead to suppressed anger and subconscious constant distraction, especially as the wearing of masks is mostly dictated and ordered by others [70,71]. These perceived interferences of integrity, self-determination and autonomy, coupled with discomfort, often contribute to substantial distraction and may ultimately be combined with the physiologically mask-related decline in psychomotoric abilities, reduced responsiveness and an overall impaired cognitive performance. It leads to misjudging situations as well as delayed, incorrect and inappropriate behavior and a decline in the effectiveness of the mask wearer [36,37,39–41].

The use of masks for several hours often causes further detectable adverse effects such as headaches, local acne, mask-associated skin irritation, itching, sensations of heat and dampness, impairments and discomfort predominantly affecting the head and face [19,29,35–37,71–73]. However, the head and face are significant for well-being due to their large representation in the sensitive cerebral cortex (homunculus) [36].

According to a questionnaire survey, masks also frequently cause anxiety and psychovegetative stress reactions in children—as well as in adults—with an increase in psychosomatic and stress-related illnesses and depressive self-experience, reduced participation, social withdrawal and lowered health-related self-care [74]. Over 50% of the mask wearers studied had at least mild depressive feelings [74]. Additional fear-inducing and often exaggerated media coverage can further intensify this. A recent retrospective analysis of the general media in the context of the 2014 Ebola epidemic showed a scientific truth content of only 38% of all publicly published information [75]. Researchers classified a total of 28% of the information as provocative and polarizing and 42% as exaggerating risks. In addition, 72% of the media content aimed to stir up health-related negative feelings. The feeling of fear, combined with insecurity and the primal human need to belong [76], causes a social dynamic that seems partly unfounded from a medical and scientific point of view.

The mask, which originally served purely hygienic purpose, has been transformed into a symbol of conformity and pseudo-solidarity. The WHO, for example, lists the advantages of the use of masks by healthy people in public to include a potentially reduced stigmatization of mask wearers, a sense of contribution to preventing the spread of the virus and a reminder to comply with other measures [2].

3.5. Psychiatric Side Effects and Dangers

As explained earlier, masks can cause increased rebreathing with an accumulation of carbon dioxide in the wearer due to increased dead space volume [16–18,20] (Figure 3), with often statistically significant measurable elevated blood carbon dioxide (CO2) levels in sufferers [13,15,17,19–28] (Figure 2). However, changes that lead to hypercapnia are known to trigger panic attacks [77,78]. This makes the significantly measurable increase in CO_2 caused by wearing a mask clinically relevant.

Interestingly, breath provocation tests by inhaling CO_2 are used to differentiate anxiety states in panic disorders and premenstrual dysphoria from other psychiatric clinical pictures. Here, absolute concentrations of 5% CO_2 already suffice to trigger panic reactions within 15–16 min [77]. The normal exhaled air content of CO_2 is about 4%.

It is obvious from experimental studies on masked subjects that concentration changes in the respiratory gases in the above-mentioned range with values above 4% could occur during rebreathing with prolonged mask use [18,23].

The activation of the locus coeruleus by CO_2 is used to generate panic reactions via respiratory gases [78,79]. This is because the locus coeruleus is an important part of the system of vegetative noradrenergic neurons, a control center in the brainstem, which reacts to an appropriate stimulus and changes in the gas concentrations in the blood by releasing the stress hormone noradrenaline [78].

From the physiological, neurological and psychological side effects and dangers described above (Sections 3.1, 3.3 and 3.4), additional problems can be derived for the use of masks in psychiatric cases. People undergoing treatment for dementia, paranoid schizophrenia, personality disorders with anxiety and panic attacks, but also panic disorders with claustrophobic components, are difficult to reconcile with a mask requirement, because even small increases in CO_2 can cause and intensify panic attacks [44,77–79].

According to a psychiatric study, patients with moderate to severe dementia have no understanding of COVID-19 protection measures and have to be persuaded to wear masks constantly [80].

According to a comparative study, patients with schizophrenia have a lower acceptance of mask-wearing (54.9% agreement) than ordinary practice patients (61.6%) [81]. The extent to which mask-wearing can lead to an exacerbation of schizophrenia symptoms has not yet been researched in detail.

When wearing masks, confusion, impaired thinking, disorientation (standardized recording via special rating and Likert scales, $p < 0.05$) and in some cases a decrease in maximum speed and reaction time (measured with the linear-position transducer, $p < 0.05$) were observed [19,32,36,38–41]. Psychotropic drugs reduce psycho-motoric functions in psychiatric patients. This can become clinically relevant especially with regard to the further reduced ability to react and the additional increased susceptibility to accidents of such patients when wearing masks.

In order to avoid an unintentional CO_2-triggered anesthesia [39], fixed and medically sedated patients, without the possibility of continuous monitoring, should not be masked according to the criteria of the Centers for Disease Control and Prevention, USA (CDC). This is because of the possible CO_2 retention described above, as there is a risk of unconsciousness, aspiration and asphyxia [16,17,20,38,82,83].

3.6. Gynaecological Side Effects and Dangers

As a critical variable, a low blood carbon dioxide level in pregnant women is maintained via an increased respiratory minute volume, stimulated by progesterone [22]. For a pregnant woman and her unborn child, there is a metabolic need for a fetal–maternal carbon dioxide (CO_2) gradient. The mother's blood carbon dioxide level should always be lower than that of the unborn child in order to ensure the diffusion of CO_2 from the fetal blood into the maternal circulation via the placenta.

Therefore, mask-related phenomena described above (Sections 3.1 and 3.2), such as the measurable changes in respiratory physiology with increased breathing resistance,

increased dead space volume (Figure 3) and the retention of exhaled carbon dioxide (CO_2) are of importance. If CO_2 is increasingly rebreathed under masks, this manifestation could, even with subliminal carbon dioxide increases, act as a disturbing variable of the fetal–maternal CO_2 gradient increasing over time of exposure and, thus, develop clinical relevance, also with regard to a reduced compensation reserve of the expectant mothers [20,22,28].

In a comparative study, 22 pregnant women wearing N95 masks during 20 min of exercise showed significantly higher percutaneous CO_2 values, with average $PtcCO_2$ values of 33.3 mmHg compared to 31.3 mmHg than in 22 pregnant women without masks ($p = 0.04$) [22]. The heat sensation of the expectant mothers was also significantly increased with masks, with $p < 0.001$ [22].

Accordingly, in another intervention study, researchers demonstrated that breathing through an N95 mask (FFP2 equivalent) impeded gas exchange in 20 pregnant women at rest and during exercise, causing additional stress on their metabolic system [28]. Thus, under an N95 mask, 20 pregnant women showed a decrease in oxygen uptake capacity VO_2 of about 14% (statistically significant, $p = 0.013$) and a decrease in carbon dioxide output capacity VCO_2 of about 18% (statistically significant, $p = 0.001$). Corresponding significant changes in exhaled oxygen and carbon dioxide equivalents were also documented with increases in exhaled carbon dioxide ($FeCO_2$) ($p < 0.001$) and decreases in exhaled oxygen (FeO_2) ($p < 0.001$), which were explained by an altered metabolism due to respiratory mask obstruction [28].

In experiments with predominantly short mask application times, neither the mothers nor the fetuses showed statistically significant increases in heart rates or changes in respiratory rates and oxygen saturation values. However, the exact effects of prolonged mask use in pregnant women remain unclear overall. Therefore, in pregnant women, extended use of surgical and N95 masks is viewed critically [20].

In addition, it is unclear whether the substances contained in industrially manufactured masks that can be inhaled over longer periods of time (e.g., formaldehyde as an ingredient of the textile and thiram as an ingredient of the ear bands) are teratogenic [20,84].

3.7. Dermatological Side Effects and Dangers

Unlike garments worn over closed skin, masks cover body areas close to the mouth and nose, i.e., body parts that are involved with respiration.

Inevitably, this leads not only to a measurable temperature rise [15,44,85], but also to a severe increase in humidity due to condensation of the exhaled air, which in turn changes the natural skin milieu considerably of perioral and perinasal areas [36,61,82]. It also increases the redness, pH-value, fluid loss through the skin epithelium, increased hydration and sebum production measurably [73]. Preexisting skin diseases are not only perpetuated by these changes, but also exacerbated. In general, the skin becomes more susceptible to infections and acne.

The authors of an experimental study were able to prove a disturbed barrier function of the skin after only 4 h of wearing a mask in 20 healthy volunteers, both for surgical masks and for N95 masks [73]. In addition, germs (bacteria, fungi and viruses) accumulate on the outside and inside of the masks due to the warm and moist environment [86–89]. They can cause clinically relevant fungal, bacterial or viral infections. The unusual increase in the detection of rhinoviruses in the sentinel studies of the German Robert Koch Institute (RKI) from 2020 [90] could be another indication of this phenomenon.

In addition, a region of the skin that is not evolutionarily adapted to such stimuli is subjected to increased mechanical stress. All in all, the above-mentioned facts cause the unfavorable dermatological effects with mask related adverse skin reactions like acne, rashes on the face and itch symptoms [91].

A Chinese research group reported skin irritation and itching when using N95 masks among 542 test participants and also a correlation between the skin damage that occurred and the time of exposure (68.9% at $\leq$6 h/day and 81.7% at >6 h/day) [92].

A New York study evaluated in a random sample of 343 participants the effects of frequent wearing of surgical mask type and N95 masks among healthcare workers during the COVID-19 pandemic. Wearing the masks caused headache in 71.4% of participants, in addition to drowsiness in 23.6%, detectable skin damage in 51% and acne in 53% of mask users [37].

On the one hand, direct mechanical skin lesions occur on the nose and cheekbones due to shear force, especially when masks are frequently put on and taken off [37,92].

On the other hand, masks create an unnaturally moist and warm local skin environment [29,36,82]. In fact, scientists were able to demonstrate a significant increase in humidity and temperature in the covered facial area in another study in which the test individuals wore masks for one hour [85]. The relative humidity under the masks was measured with a sensor (Atmo-Tube, San Francisco, CA, USA). The sensation of humidity and temperature in the facial area is more crucial for well-being than other body regions [36,44]. This can increase discomfort under the masks. In addition, the increase in temperature favors bacterial optimization.

The pressure of the masks also causes an obstruction of the flow physiology of lymph and blood vessels in the face, with the consequence of increased disturbance of skin function [73] and ultimately also contributing to acne in up to 53% of all wearers and other skin irritations in up to 51% of all wearers [36,37,82].

Other researchers examined 322 participants with N95 masks in an observational study and detected acne in up to 59.6% of them, itching in 51.4% and redness in 35.8% as side effects [72].

In up to 19.6% (273) of the 1393 wearers of different masks (community masks, surgical, N95 masks), itching could be objectified in one study, in 9% even severely. An atopic predisposition (allergy tendency) correlated with the risk of itching. The length of use was significantly related to the risk of itching ($p < 0.0001$) [93].

In another dermatological study from 2020, 96.9% of 876 users of all mask types (community masks, surgical masks, N95 masks) confirmed adverse problems with a significant increase in itching (7.7%), accompanied by fogging-up of glasses (21.3%), flushing (21.3%), slurred speech (12.3%) and difficulty breathing (35.9%) ($p < 0.01$) [71].

Apart from an increased incidence of acne [37,72,91] under masks, contact eczema and urticaria [94] are generally described in connection with hypersensitivities to ingredients of the industrially manufactured masks (surgical mask and N95) such as formaldehyde (ingredient of the textile) and thiram (ingredient of the ear bands) [73,84]. The hazardous substance thiram, originally a pesticide and corrosive, is used in the rubber industry as a optimization accelerator. Formaldehyde is a biocide and carcinogen and is used as a disinfectant in the industry.

Even isolated permanent hyperpigmentation as a result of post-inflammatory or pigmented contact dermatitis has been described by dermatologists after prolonged mask use [72,91].

3.8. ENT and Dental Side Effects and Dangers

There are reports from dental communities about negative effects of masks and are accordingly titled "mask mouth" [95]. Provocation of gingivitis (inflammation of the gums), halitosis (bad breath), candidiasis (fungal infestation of the mucous membranes with Candida albicans) and cheilitis (inflammation of the lips), especially of the corners of the mouth, and even plaque and caries are attributed to the excessive and improper use of masks. The main trigger of the oral diseases mentioned is an increased dry mouth due to a reduced saliva flow and increased breathing through the open mouth under the mask. Mouth breathing causes surface dehydration and reduced salivary flow rate (SFR) [95]. Dry mouth is scientifically proven due to mask wear [29]. The bad habit of breathing through the open mouth while wearing a mask seems plausible because such breathing pattern compensates for the increased breathing resistance, especially when inhaling through the masks [60,61]. In turn, the outer skin moisture [71,73,85] with altered

skin flora, which has already been described under dermatological side effects (Section 3.7), is held responsible as an explanation for the inflammation of the lips and corners of the mouth (cheilitis) [95]. This clearly shows the disease-promoting reversal of the natural conditions caused by masks. The physiological internal moisture with external dryness in the oral cavity converts into internal dryness with external moisture.

ENT physicians recently discovered a new form of irritant rhinitis due to N95 mask use in 46 patients. They performed endoscopies and nasal irrigations on mask wearers, which were subsequently assessed pathologically. Clinical problems were recorded with standardized questionnaires. They found statistically significant evidence of mask-induced rhinitis and itching and swelling of the mucous membranes as well as increased sneezing ($p < 0.01$). Endoscopically, it showed an increased secretion and evidence of inhaled mask polypropylene fibers as the trigger of mucosal irritation [96].

In a study of 221 health care workers, ENT physicians objectified a voice disorder in 33% of mask users. The VHI-10 score of 1 to 10, which measures voice disorders, was on average 5.72 higher in these mask users (statistically significant with $p < 0.001$). The mask not only acted as an acoustic filter, provoking excessively loud speech, it also seems to trigger impaired vocal cord coordination because the mask compromises the pressure gradients required for undisturbed speech [43]. The researchers concluded from their findings that masks could pose a potential risk of triggering new voice disorders as well as exacerbating existing ones.

3.9. Sports Medicine Side Effects and Dangers

According to the literature, performance-enhancing effects of masks regarding cardiovascular optimization and improvement of oxygen uptake capacity cannot be proven.

For example, in an experimental reference study (12 subjects per group), the training mask that supposedly mimics altitude training (ETM: elevation training mask) only had training effects on the respiratory muscles. However, mask wearers showed significantly lower oxygen saturation values (SpO_2%) during exercise (SpO_2 of 94% for mask wearers versus 96% for mask-less, $p < 0.05$) [33], which can be explained by an increased dead space volume and increased resistance during breathing. The measured oxygen saturation values were significantly lower than the normal values in the group of mask wearers, which indicates a clinical relevance.

The proven adaptation effect of the respiratory muscles in healthy athletes [33] clearly suggests that masks have a disruptive effect on respiratory physiology.

In another intervention study on mask use in weightlifters, researchers documented statistically significant effects of reduced attention (questionnaire recording, Likert scale) and a slowed maximum speed of movement detectable by means of sensors (both significant at $p < 0.001$), leading the researchers to conclude that mask use in sport is not without risks. As a secondary finding, they also detected a significant decrease in oxygen saturation SpO_2 when performing special weight-lifting exercises ("back squats") in the mask group after only 1 min of exercise compared to the mask-free group ($p < 0.001$) [32]. The proven tendency of the masks to shift the chemical parameter oxygen saturation SpO_2 in a pathological direction (lower limit value 95%) may well have clinical relevance in untrained or sick individuals.

Sports medicine confirmed an increase in carbon dioxide (CO_2) retention, with an elevation in CO_2 partial pressure in the blood with larger respiratory dead space volumes [14].

In fact, dead space-induced CO_2 retention while wearing a mask during exercise was also experimentally proven. The effects of a short aerobic exercise under N95 masks were tested on 16 healthy volunteers. A significantly increased end-expiratory partial pressure of carbon dioxide ($PETCO_2$) with plus 8 mmHg ($p < 0.001$) was found [24]. The increase in blood carbon dioxide (CO_2) in the mask wearers under maximum load was plus 14% CO_2 for surgical masks and plus 23% CO_2 for N95 masks, an effect that may well have clinical relevance in the pre-diseased, elderly and children, as these values strongly approached the pathological range [24].

In an interesting endurance study with eight middle-aged subjects (19–66), the gas content for O_2 and CO_2 under the masks was determined before and after exercise. Even at rest, the oxygen availability under the masks was 13% lower than without the masks and the carbon dioxide (CO_2) concentration was 30 times higher. Under stress (Ruffier test), the oxygen concentration (% O_2) below the mask dropped significantly by a further 3.7%, while the carbon dioxide concentration (% CO_2) increased significantly by a further 20% (statistically significant with $p < 0.001$). Correspondingly, the oxygen saturation of the blood (SpO_2) of the test persons also decreased significantly from 97.6 to 92.1% ($p < 0.02$) [18]. The drop in the oxygen saturation value (SpO_2) to 92%, clearly below the normal limit of 95%, is to be classified as clinically relevant and detrimental to health.

These facts are an indication that the use of masks also triggers the effects described above leading to hypoxia and hypercapnia in sports. Accordingly, the WHO and Centers for Disease Control and Prevention, GA, USA (CDC) advise against wearing masks during physical exercise [82,97].

3.10. Social and Sociological Side Effects and Dangers

The results of a Chilean study with health care workers show that masks act like an acoustic filter and provoke excessively loud speech. This causes a voice disorder [43]. The increased volume of speech also contributes to increased aerosol production by the mask wearer [98]. These experimental data measured with the Aerodynamic Particle Sizer (APS, TSI, model 332, TSI Incorporated, Minnesota, MI, USA) are highly relevant.

Moreover, mask wearers are prevented from interacting normally in everyday life due to impaired clarity of speech [45], which tempts them to get closer to each other.

This results in a distorted prioritization in the general public, which counteracts the recommended measures associated with the COVID-19 pandemic. The WHO prioritizes social distancing and hand hygiene with moderate evidence and recommends wearing a mask with weak evidence, especially in situations where individuals are unable to maintain a physical distance of at least 1 m [3].

The disruption of non-verbal communication due to the loss of facial expression recognition under the mask can increase feelings of insecurity, discouragement and numbness as well as isolation, which can be extremely stressful for the mentally and hearing-impaired [16].

Experts point out that masks disrupt the basics of human communication (verbal and nonverbal). The limited facial recognition caused by masks leads to a suppression of emotional signals. Masks, therefore, disrupt social interaction, erasing the positive effect of smiles and laughter but at the same time greatly increasing the likelihood of misunderstandings because negative emotions are also less evident under masks [42].

A decrease in empathy perception through mask use with disruption of the doctor–patient relationship has already been scientifically proven on the basis of a randomized study (statistically significant, with $p = 0.04$) [99]. In this study, the Consultation Empathy Care Measury, the Patient Enablement Instrument (PEI) Score and a Satisfaction Rating Scale were assessed in 1030 patients. The 516 doctors, who wore masks throughout, conveyed reduced empathy towards the patients and, thus, nullified the positive health-promoting effects of a dynamic relationship. These results demonstrate a disruption of interpersonal interaction and relationship dynamics caused by masks.

The WHO guidance on the use of masks in children in the community, published in August 2020, points out that the benefits of mask use in children must be weighed up against the potential harms, including social and communicational concerns [100].

Fears that widespread pandemic measures will lead to dysfunctional social life with degraded social, cultural and psychological interactions have also been expressed by other experts [6–8,42].

3.11. Social and Occupational Medicine Side Effects and Hazards

In addition to mask-specific complaints such as a feeling of heat, dampness, shortness of breath and headache, various physiological phenomena were documented, such as the significant increase in heart and respiratory rate, the impairment of lung function parameters, the decrease in cardiopulmonary capacity (e.g., lower maximum blood lactate response) [15,19,21,23,29–31], as well as the changes in oxygen and carbon dioxide both in the end-expiratory and the air under the mask that was measured in the blood of the individuals [13,15,18,19,21–25,27–34]. The significant changes were measurable after only a few minutes of wearing a mask and in some cases reached magnitudes of minus 13% reduced O_2 concentration and 30-fold increased CO_2 concentration of the inhaled air under masks ($p < 0.001$) [18]. The changes observed were not only statistically significant, but also clinically relevant; the subjects also showed pathological oxygen saturation after exposure to masks ($p < 0.02$) [18].

Shortness of breath during light exertion (6 min walking) under surgical masks has been recorded with statistical significance in 44 healthy subjects in a prospective experimental intervention study ($p < 0.001$) [101]. Here, the complaints were assessed using a subjective, visual analogue scale.

In another study from 2011, all tested masks caused a significantly measurable increase in discomfort and a feeling of exhaustion in the 27 subjects during prolonged usage ($p < 0.0001$) [69].

These symptoms lead to additional stress for the occupational mask wearer and, thus, in relation to the feeling of exhaustion, contribute to the self-perpetuating vicious circle caused by the vegetative sympathetic activation, which further increases the respiratory and heart rate, blood pressure and increased sense of exhaustion [16,20,35,83].

Other studies showed that the psychological and physical effects of the masks can lead to an additional reduction in work performance (measured with the Roberge Subjective Symptoms-during-Work Scale, a Likert scale of 1–5) via increased feelings of fatigue, dissatisfaction and anxiety [58,102,103].

Wearing masks over a longer period of time also led to physiological and psychological impairments in other studies and, thus, reduced work performance [19,36,58,69]. In experiments on respiratory-protective equipment, an increase in the dead space volume by 350 mL leads to a reduction in the possible performance/time by approx. −19%, furthermore to a decrease in breathing comfort by −18% (measured via a subjective rating scale) [58]. In addition, the time spent working and the flow of work is interrupted and reduced by putting on and taking off the masks and changing them. The reduced work performance has been recorded in the literature found as described above (especially in Sections 3.1 and 3.2) but has not been quantified further in detail [36,58].

Surgical mask type and N95 protective equipment frequently caused adverse effects in medical personnel such as headaches, breathing difficulties, acne, skin irritation, itching, decreased alertness, decreased mental performance and feelings of dampness and heat [19,29,37,71,85]. Subjective, work performance-reducing, mask-related impairments in users, measured with special survey scores and Likert scales, have also been described in other studies [15,21,27,32,35,43,66–68,72,96,99].

In Section 3.7 on dermatology, we already mentioned a paper that demonstrated a significant temperature increase of 1.9 °C on average (to over 34.5 °C) in the mask-covered facial area ($p < 0.05$) [85]. Due to the relatively larger representation in the sensitive cerebral cortex (homunculus), the temperature sensation in the face is more decisive for the feeling of well-being than other body regions [36,44]. The perception of discomfort when wearing a mask can, thus, be intensified. Interestingly, in our analysis, we found a combined occurrence of the physical variable temperature rise under the mask and the symptom respiratory impairment in seven of eight studies concerned, with a mutual significantly measured occurrence in 88%. We also detected a combined occurrence of significantly measured temperature rise under the mask and significantly measured fatigue in 50% of the relevant primary studies (three of six papers, Figure 2). These clustered associations of

temperature rise with symptoms of respiratory impairment and fatigue suggest a clinical relevance of the detected temperature rise under masks. In the worst case scenario, the effects mentioned can reinforce each other and lead to decompensation, especially in the presence of COPD, heart failure and respiratory insufficiency.

The sum of the disturbances and discomforts that can be caused by a mask also contributes to distraction (see also psychological impairment). These, in conjunction with a decrease in psycho-motoric skills, reduced responsiveness and overall impaired cognitive performance (all of which are pathophysiological effects of wearing a mask) [19,29,32,39–41] can lead to a failure to recognize hazards and, thus, to accidents or avoidable errors at work [19,36,37]. Of particular note here are mask-induced listlessness ($p < 0.05$), impaired thinking ($p < 0.05$) and concentration problems ($p < 0.02$) as measured by a Likert scale (1–5) [29]. Accordingly, occupational health regulations take action against such scenarios. The German Industrial Accident Insurance (DGUV) has precise and extensive regulations for respiratory protective equipment where they document the limitation of wearing time, levels of work intensity and defined instruction obligation [104].

The standards and norms prescribed in many countries regarding different types of masks to protect their workers are also significant from an occupational health point of view [105]. In Germany, for example, there are very strict safety specifications for masks from other international countries. These specify the requirements for the protection of the wearer [106]. All these standards and the accompanying certification procedures were increasingly relaxed with the introduction of mandatory masks for the general public. This meant that non-certified masks such as community masks were also used on a large scale in the work and school sectors for longer periods during the pandemic measures [107]. Most recently, in October 2020, the German Social Accident Insurance (DGUV) recommended the same usage time limits for community masks as for filtering half masks, namely, a maximum of three shifts of 120 min per day with recovery breaks of 30 min in between. In Germany, FFP2 (N95) masks must be worn for 75 min, followed by a 30-minute break. An additional suitability examination by specialized physicians is also obligatory and stipulated for occupationally used respirators [104].

3.12. Microbiological Consequences for Wearer and Environment: Foreign/Self-Contamination

Masks cause retention of moisture [61]. Poor filtration performance and incorrect use of surgical masks and community masks, as well as their frequent reuse, imply an increased risk of infection [108–110]. The warm and humid environment created by and in masks without the presence of protective mechanisms such as antibodies, the complement system, defense cells and pathogen-inhibiting and on a mucous membrane paves the way for unimpeded growth and, thus, an ideal growth and breeding ground for various pathogens such as bacteria and fungi [88] and also allows viruses to accumulate [87]. The warm and humid mask microclimate favors the accumulation of various germs on and underneath the masks [86], and the germ density is measurably proportional to the length of time the mask is worn. After only 2 h of wearing the mask, the pathogen density increases almost tenfold in experimental observation studies [87,89].

From a microbiological and epidemiological point of view, masks in everyday use pose a risk of contamination. This can occur as foreign contamination but also as self-contamination. On the one hand, germs are sucked in or attach themselves to the masks through convection currents. On the other hand, potential infectious agents from the nasopharynx accumulate excessively on both the outside and inside of the mask during breathing [5,88]. This is compounded by contact with contaminated hands. Since masks are constantly penetrated by germ-containing breath and the pathogen reproduction rate is higher outside mucous membranes, potential infectious pathogens accumulate excessively on the outside and inside of masks. On and in the masks, there are quite serious, potentially disease-causing bacteria and fungi such as *E. coli* (54% of all germs detected), Staphylococcus aureus (25% of all germs detected), Candida (6%), Klebsiella (5%), Enterococci (4%),

Pseudomonads (3%), Enterobacter (2%) and Micrococcus (1%) even detectable in large quantities [88].

In another microbiological study, the bacterium Staphylococcus aureus (57% of all bacteria detected) and the fungus Aspergillus (31% of all fungi detected) were found to be the dominant germs on 230 surgical masks examined [86].

After more than six hours of use, the following viruses were found in descending order on 148 masks worn by medical personnel: adenovirus, bocavirus, respiratory syncytial virus and influenza viruses [87].

From this aspect, it is also problematic that moisture distributes these potential pathogens in the form of tiny droplets via capillary action on and in the mask, whereby further proliferation in the sense of self- and foreign contamination by the aerosols can then occur internally and externally with every breath [35]. In this regard, it is also known from the literature that masks are responsible for a proportionally disproportionate production of fine particles in the environment and, surprisingly, much more so than in people without masks [98].

It was shown that all mask-wearing subjects released significantly more smaller particles of size 0.3–0.5 µm into the air than mask-less people, both when breathing, speaking and coughing (fabric, surgical, N95 masks, measured with the Aerodynamic Particle Sizer, APS, TS, model 3329) [98]. The increase in the detection of rhinoviruses in the sentinel studies of the German RKI from 2020 [90] could be a further indication of this phenomenon, as masks were consistently used by the general population in public spaces in that year.

3.13. Epidemiological Consequences

The possible side effects and dangers of masks described in this paper are based on studies of different types of masks. These include the professional masks of the surgical mask type and N95/KN95 (FFP2 equivalent) that are commonly used in everyday life, but also the community fabric masks that were initially used. In the case of N95, the N stands for National Institute for Occupational Safety and Health of the United States (NIOSH), and 95 indicates the 95 per cent filtering capacity for fine particles up to at least 0.3 µm [82].

A major risk of mask use in the general public is the creation of a false sense of security with regard to protection against viral infections, especially in the sense of a falsely assumed strong self-protection. Disregarding infection risks may not only neglect aspects of source control, but also result in other disadvantages. Although there are quite a few professional positive accounts of the widespread use of masks in the general populace [111], most of the serious and evident scientific reports conclude that the general obligation to wear masks conveys a false sense of security [4,5]. However, this leads to a neglect of those measures that, according to the WHO, have a higher level of effectiveness than mask-wearing: social distancing and hand hygiene [2,112]. Researchers were able to provide statistically significant evidence of a false sense of security and more risky behavior when wearing masks in an experimental setting [112].

Decision makers in many countries informed their citizens early on in the pandemic in March 2020 that people without symptoms should not use a medical mask, as this created a false sense of security [113]. The recommendation was ultimately changed in many countries. At least Germany pointed out that wearers of certain types of masks such as the common fabric masks (community masks) cannot rely on them to protect them or others from transmission of SARS-CoV-2 [114].

However, scientists not only complain about the lack of evidence for fabric masks in the scope of a pandemic [16,110], but also about the high permeability of fabric masks with particles and the potential risk of infection they pose [108,109]. Ordinary fabric masks with a 97% penetration for particle dimensions of $\geq$0.3 µm are in stark contrast to medical-type surgical masks with a 44% penetration. In contrast, the N95 mask has a penetration rate of less than 0.01% for particles $\geq$ 0.3 µm in the laboratory experiment [108,115].

For the clinical setting in hospitals and outpatient clinics, the WHO guidelines recommend only surgical masks for influenza viruses for the entire patient treatment except for the strongly aerosol-generating measures, for which finer filtering masks of the type N95 are suggested. However, the WHO's endorsement of specific mask types is not entirely evidence-based due to the lack of high-quality studies in the health sector [108,109,116,117].

In a laboratory experiment (evidence level IIa study), it was demonstrated that both surgical masks and N95 masks have deficits in protection against SARS-CoV-2 and influenza viruses using virus-free aerosols [118]. In this study, the FFP2-equivalent N95 mask performed significantly better in protection (8–12 times more effective) than the surgical mask, but neither mask type established reliable, hypothesis-generated protection against corona and influenza viruses. Both mask types could be penetrated unhindered by aerosol particles with a diameter of 0.08 to 0.2 µm. Both the SARS-CoV-2 pathogens with a size of 0.06 to 0.14 µm [119] and the influenza viruses with 0.08 to 0.12 µm are unfortunately well below the mask pore sizes [118].

The filtering capacity of the N95 mask up to 0.3 µm [82] is usually not achieved by surgical masks and community masks. However, aerosol droplets, which have a diameter of 0.09 to 3 µm in size, are supposed to serve as a transport medium for viruses. These also penetrate the medical masks by 40%. Often, there is also a poor fit between the face and the mask, which further impairs their function and safety [120]. The accumulation of aerosol droplets on the mask is problematic. Not only do they absorb nanoparticles such as viruses [6], but they also follow the airflow when inhaling and exhaling, causing them to be carried further. In addition, a physical decay process has been described for aerosol droplets at increasing temperatures, as also occurs under a mask [15,44,85]. This process can lead to a decrease in size of the fine water droplets up to the diameter of a virus [121,122]. The masks filter larger aerosol droplets but cannot retain viruses themselves and such smaller, potentially virus-containing aerosol droplets of less than 0.2 µm and hence cannot stop the spread of virus [123].

Similarly, in an in vivo comparative studies of N95 and surgical masks, there were no significant differences in influenza virus infection rates [124,125]. Although this contrasts with encouraging in vitro laboratory results with virus-free aerosols under non-natural conditions, even with fabric masks [126], it should be noted that under natural in-vivo conditions, the promising filtration functions of fabric masks based on electrostatic effects also rapidly diminish under increasing humidity [127]. A Swiss textile lab test of various masks available on the market to the general public recently confirmed that most mask types filter aerosols insufficiently. For all but one of the eight reusable fabric mask types tested, the filtration efficacy according to EN149 was always less than 70% for particles of 1 µm in size. For disposable masks, only half of all eight mask types tested were efficient enough at filtering to retain 70% of particles 1 µm in size [128].

A recent experimental study even demonstrated that all mask-wearing people (surgical, N95, fabric masks) release significantly and proportionately smaller particles of size 0.3 to 0.5 µm into the air than mask-less people, both when breathing, speaking and coughing [98]. According to this, the masks act like nebulizers and contribute to the production of very fine aerosols. Smaller particles, however, spread faster and further than large ones for physical reasons. Of particular interest in this experimental reference study was the finding that a test subject wearing a single-layer fabric mask was also able to release a total of 384% more particles (of various sizes) when breathing than a person without [98].

It is not only the aforementioned functional weaknesses of the masks themselves that lead to problems, but also their use. This increases the risk of a false sense of security. According to the literature, mistakes are made by both healthcare workers and lay people when using masks as hygienically correct mask use is by no means intuitive. Overall, 65% of healthcare professionals and as many as 78% of the general population, use masks incorrectly [116]. With both surgical masks and N95 masks, adherence to the rules of use is impaired and not adequately followed due to reduced wearability with heat discomfort and skin irritation [29,35,116,129]. This is exacerbated by the accumulation of carbon dioxide

due to the dead space (especially under the N95 masks) with the resulting headaches described [19,27,37,66–68,83]. Increased heart rate, itching and feelings of dampness [15,29,30,35,71] also lead to reduced safety and quality during use (see also social and occupational health side effects and hazards). For this reason, (everyday) masks are even considered a general risk for infection in the general population, which does not come close to imitating the strict hygiene rules of hospitals and doctors' offices: the supposed safety, thus, becomes a safety risk itself [5].

In a meta-analysis of evidence level Ia commissioned by the WHO, no effect of masks in the context of influenza virus pandemic prevention could be demonstrated [130]. In 14 randomized controlled trials, no reduction in the transmission of laboratory-confirmed influenza infections was shown. Due to the similar size and distribution pathways of the virus species (influenza and Corona, see above), the data can also be transferred to SARS-CoV-2 [118]. Nevertheless, a combination of occasional mask-wearing with adequate hand-washing caused a slight reduction in infections for influenza in one study [131]. However, since no separation of hand hygiene and masks was achieved in this study, the protective effect can rather be attributed to hand hygiene in view of the aforementioned data [131].

A recently published large prospective Danish comparative study comparing mask wearers and non-mask wearers in terms of their infection rates with SARS-CoV2 could not demonstrate any statistically significant differences between the groups [132].

3.14. *Paediatric Side Effects and Hazards*

Children are particularly vulnerable and may be more likely to receive inappropriate treatment or additional harm. It can be assumed that the potential adverse mask effects described for adults are all the more valid for children (see Section 3.1 to Section 3.13: physiological internal, neurological, psychological, psychiatric, dermatological, ENT, dental, sociological, occupational and social medical, microbiological and epidemiological impairments and also Figures 2 and 3).

Special attention must be paid to the respiration of children, which represents a critical and vulnerable physiological variable due to higher oxygen demand, increased hypoxia susceptibility of the CNS, lower respiratory reserve, smaller airways with a stronger increase in resistance when the lumen is narrowed. The diving reflex caused by stimulating the nose and upper lip can cause respiratory arrest to bradycardia in the event of oxygen deficiency.

The masks currently used for children are exclusively adult masks manufactured in smaller geometric dimensions and had neither been specially tested nor approved for this purpose [133].

In an experimental British research study, the masks frequently led to feelings of heat ($p < 0.0001$) and breathing problems ($p < 0.03$) in 100 school children between 8 and 11 years of age especially during physical exertion, which is why the protective equipment was taken off by 24% of the children during physical activity [133]. The exclusion criteria for this mask experiment were lung disease, cardiovascular impairment and claustrophobia [133].

Scientists from Singapore were able to demonstrate in their level Ib study published in the renowned journal "nature" that 106 children aged between 7 and 14 years who wore FFP2 masks for only 5 min showed an increase in the inspiratory and expiratory CO_2 levels, indicating disturbed respiratory physiology [26].

However, a disturbed respiratory physiology in children can have long-term disease-relevant consequences. Slightly elevated CO_2 levels are known to increase heart rate, blood pressure, headache, fatigue and concentration disorders [38].

Accordingly, the following conditions were listed as exclusion criteria for mask use [26]: any cardiopulmonary disease including but not limited to: asthma, bronchitis, cystic fibrosis, congenital heart disease, emphysema; any condition that may be aggravated by physical exertion, including but not limited to: exercise-induced asthma; lower respiratory tract infections (pneumonia, bronchitis within the last 2 weeks), anxiety disorders,

diabetes, hypertension or epilepsy/attack disorder; any physical disability due to medical, orthopedic or neuromuscular disease; any acute upper respiratory illness or symptomatic rhinitis (nasal obstruction, runny nose or sneezing); any condition with deformity that affects the fit of the mask (e.g., increased facial hair, craniofacial deformities, etc.).

It is also important to emphasize the possible effects of masks in neurological diseases, as described earlier (Section 3.3).

Both masks and face shields caused fear in 46% of children (37 out of 80) in a scientific study. If children are given the choice of whether the doctor examining them should wear a mask they reject this in 49% of the cases. Along with their parents, the children prefer the practitioner to wear a face visor (statistically significant with $p < 0.0001$) [134].

A recent observational study of tens of thousands of mask-wearing children in Germany helped the investigators objectify complaints of headaches (53%), difficulty concentrating (50%), joylessness (49%), learning difficulties (38%) and fatigue in 37% of the 25,930 children evaluated. Of the children observed, 25% had new onset anxiety and even nightmares [135]. In children, the threat scenarios generated by the environment are further maintained via masks, in some cases, even further intensified, and in this way, existing stress is intensified (presence of subconscious fears) [16,35,136,137].

This can in turn lead to an increase in psychosomatic and stress-related illnesses [74,75]. For example, according to an evaluation, 60% of mask wearers showed stress levels of the highest grade 10 on a scale of 1 to a maximum of 10. Less than 10% of the mask wearers surveyed had a stress level lower than 8 out of a possible 10 [74].

As children are considered a special group, the WHO also issued a separate guideline on the use of masks in children in the community in August 2020, explicitly advising policy makers and national authorities, given the limited evidence, that the benefits of mask use in children must be weighed up against the potential harms associated with mask use. This includes feasibility and discomfort, as well as social and communication concerns [100].

According to experts, masks block the foundation of human communication and the exchange of emotions and not only hinder learning but deprive children of the positive effects of smiling, laughing and emotional mimicry [42]. The effectiveness of masks in children as a viral protection is controversial, and there is a lack of evidence for their widespread use in children; this is also addressed in more detail by the scientists of the German University of Bremen in their thesis paper 2.0 and 3.0 [138].

3.15. *Effects on the Environment*

According to WHO estimates of a demand of 89 million masks per month, their global production will continue to increase under the Corona pandemic [139]. Due to the composition of, e.g., disposable surgical masks with polymers such as polypropylene, polyurethane, polyacrylonitrile, polystyrene, polycarbonate, polyethylene and polyester [140], an increasing global challenge, also from an environmental point of view, can be expected, especially outside Europe, in the absence of recycling and disposal strategies [139]. The aforementioned single use polymers have been identified as a significant source of plastic and plastic particles for the pollution of all water cycles up to the marine environment [141].

A significant health hazard factor is contributed by mask waste in the form of microplastics after decomposition into the food chain. Likewise, contaminated macroscopic disposable mask waste—especially before microscopic decay—represents a widespread medium for microbes (protozoa, bacteria, viruses, fungi) in terms of invasive pathogens [86–89,142]. Proper disposal of bio-contaminated everyday mask material is insufficiently regulated even in western countries.

4. Discussion

The potential drastic and undesirable effects found in multidisciplinary areas illustrate the general scope of global decisions on masks in general public in the light of combating the pandemic. According to the literature found, there are clear, scientifically recorded adverse effects for the mask wearer, both on a psychological and on a social and physical level.

Neither higher level institutions such as the WHO or the European Centre for Disease Prevention and Control (ECDC) nor national ones, such as the Centers for Disease Control and Prevention, GA, USA (CDC) or the German RKI, substantiate with sound scientific data a positive effect of masks in the public (in terms of a reduced rate of spread of COVID-19 in the population) [2,4,5].

Contrary to the scientifically established standard of evidence-based medicine, national and international health authorities have issued their theoretical assessments on the masks in public places, even though the compulsory wearing of masks gives a deceptive feeling of safety [5,112,143].

From an infection epidemiological point of view, masks in everyday use offer the risk of self-contamination by the wearer from both inside and outside, including via contaminated hands [5,16,88]. In addition, masks are soaked by exhaled air, which potentially accumulates infectious agents from the nasopharynx and also from the ambient air on the outside and inside of the mask. In particular, serious infection-causing bacteria and fungi should be mentioned here [86,88,89], but also viruses [87]. The unusual increase in the detection of rhinoviruses in the sentinel studies of the German RKI from 2020 [90] could be an indication of this phenomenon. Clarification through further investigations would therefore be desirable.

Masks, when used by the general public, are considered by scientists to pose a risk of infection because the standardized hygiene rules of hospitals cannot be followed by the general public [5]. On top of that, mask wearers (surgical, N95, fabric masks) exhale relatively smaller particles (size 0.3 to 0.5 µm) than mask-less people and the louder speech under masks further amplifies this increased fine aerosol production by the mask wearer (nebulizer effect) [98].

The history of modern times shows that already in the influenza pandemics of 1918–1919, 1957–58, 1968, 2002, in SARS 2004–2005 as well as with the influenza in 2009, masks in everyday use could not achieve the hoped-for success in the fight against viral infection scenarios [67,144]. The experiences led to scientific studies describing as early as 2009 that masks do not show any significant effect with regard to viruses in an everyday scenario [129,145]. Even later, scientists and institutions rated the masks as unsuitable to protect the user safely from viral respiratory infections [137,146,147]. Even in hospital use, surgical masks lack strong evidence of protection against viruses [67].

Originally born out of the useful knowledge of protecting wounds from surgeons' breath and predominantly bacterial droplet contamination [144,148,149], the mask has been visibly misused with largely incorrect popular everyday use, particularly in Asia in recent years [150]. Significantly, the sociologist Beck described the mask as a cosmetic of risk as early as 1992 [151]. Unfortunately, the mask is inherent in a vicious circle: strictly speaking, it only protects symbolically and at the same time represents the fear of infection. This phenomenon is reinforced by the collective fear mongering, which is constantly nurtured by main stream media [137].

Nowadays, the mask represents a kind of psychological support for the general population during the virus pandemic, promising them additional anxiety-reduced freedom of movement. The recommendation to use masks in the sense of "source control" not out of self-protection but out of "altruism" [152] is also very popular with the regulators as well as the population of many countries. The WHO's recommendation of the mask in the current pandemic is not only a purely infectiological approach, but is also clear on the possible advantages for healthy people in the general public. In particular, a reduced potential stigmatization of mask wearers, the feeling of a contribution made to preventing the spread of the virus, as well as the reminder to adhere to other measures are mentioned [2].

It should not go unmentioned that very recent data suggest that the detection of SARS-CoV-2 infection does not seem to be directly related to popular mask use. The groups examined in a retrospective comparative study (infected with SARS-CoV-2 and not infected) did not differ in their habit of using masks: approximately 70% of the subjects in both groups always wore masks and another 14.4% of them frequently [143].

In a Danish prospective study on mask-wearing carried out on about 6000 participants and published in 2020, scientists found no statistically significant difference in the rates of SARS-CoV-2 infection when comparing the group of 3030 mask wearers with the 2994 maskless participants in the study ($p = 0.38$) [132].

Indeed, in the case of viral infections, masks appear to be not only less effective than expected, but also not free of undesirable biological, chemical, physical and psychological side effects [67]. Accordingly, some experts claim that well-intentioned unprofessionalism can be quite dangerous [6].

The dermatological colleagues were the first to describe common adverse effects of mask-wearing in larger collectives. Simple, direct physical, chemical and biological effects of the masks with increases in temperature, humidity and mechanical irritation caused acne in up to 60% of wearers [37,71–73,85]. Other significantly documented consequences were eczema, skin damage and overall impaired skin barrier function [37,72,73].

These direct effects of mask use are an important pointer to further detrimental effects affecting other organ systems.

In our work, we have identified scientifically validated and numerous statistically significant adverse effects of masks in various fields of medicine, especially with regard to a disruptive influence on the highly complex process of breathing and negative effects on the respiratory physiology and gas metabolism of the body (see Figures 2 and 3). The respiratory physiology and gas exchange play a key role in maintaining a health-sustaining balance in the human body [136,153]. According to the studies we found, a dead space volume that is almost doubled by wearing a mask and a more than doubled breathing resistance (Figure 3) [59–61] lead to a rebreathing of carbon dioxide with every breathing cycle [16–18,39,83] with—in healthy people mostly—a subthreshold but, in sick people, a partly pathological increase in the carbon dioxide partial pressure ($PaCO_2$) in the blood [25,34,58]. According to the primary studies found, these changes contribute reflexively to an increase in respiratory frequency and depth [21,23,34,36] with a corresponding increase in the work of the respiratory muscles via physiological feedback mechanisms [31,36]. Thus, it is not, as initially assumed, purely positive training through mask use. This often increases the subliminal drop in oxygen saturation SpO_2 in the blood [23,28–30,32], which is already reduced by increased dead space volume and increased breathing resistance [18,31].

The overall possible resulting measurable drop in oxygen saturation O_2 of the blood on the one hand [18,23,28–30,32] and the increase in carbon dioxide (CO_2) on the other [13,15,19,21–28] contribute to an increased noradrenergic stress response, with heart rate increase [29,30,35] and respiratory rate increase [15,21,23,34], in some cases also to a significant blood pressure increase [25,35].

In panic-prone individuals, stress-inducing noradrenergic sympathetic activation can be partly directly mediated via the carbon dioxide (CO_2) mechanism at the locus coeruleus in the brainstem [39,78,79,153], but also in the usual way via chemo-sensitive neurons of the nucleus solitarius in the medulla [136,154]. The nucleus solitarius [136] is located in the deepest part of the brainstem, a gateway to neuronal respiratory and circulatory control [154]. A decreased oxygen (O_2) blood level there causes the activation of the sympathetic axis via chemoreceptors in the carotids [155,156].

Even subthreshold changes in blood gases such as those provoked when wearing a mask cause reactions in these control centers in the central nervous system. Masks, therefore, trigger direct reactions in important control centers of the affected brain via the slightest changes in oxygen and carbon dioxide in the blood of the wearer [136,154,155].

A link between disturbed breathing and cardiorespiratory diseases such as hypertension, sleep apnea and metabolic syndrome has been scientifically proven [56,57]. Interestingly, decreased oxygen/O_2 blood levels and also increased carbon dioxide/CO_2 blood levels are considered the main triggers for the sympathetic stress response [38,136]. The aforementioned chemo-sensitive neurons of the nucleus solitarius in the medulla are considered to be the main responsible control centers [136,154,155]. Clinical effects of prolonged mask-wearing would, thus, be a conceivable intensification of chronic stress re-

actions and negative influences on the metabolism leading towards a metabolic syndrome. The mask studies we found show that such disease-relevant respiratory gas changes (O_2 and CO_2) [38,136] are already achieved by wearing a mask [13,15,18,19,21–34].

A connection between hypoxia, sympathetic reactions and leptin release is scientifically known [136].

Additionally important is the connection of breathing with the influence on other bodily functions [56,57], including the psyche with the generation of positive emotions and drive [153]. The latest findings from neuro-psychobiological research indicate that respiration is not only a function regulated by physical variables to control them (feedback mechanism), but rather independently influences higher-level brain centers and, thus, also helps to shape psychological and other bodily functions and reactions [153,157,158]. Since masks impede the wearer's breathing and accelerate it, they work completely against the principles of health-promoting breathing [56,57] used in holistic medicine and yoga. According to recent research, undisturbed breathing is essential for happiness and healthy drive [157,159], but masks work against this.

The result of significant changes in blood gases in the direction of hypoxia (drop in oxygen saturation) and hypercapnia (increase in carbon dioxide concentration) through masks, thus, has the potential to have a clinically relevant influence on the human organism even without exceeding normal limits.

According to the latest scientific findings, blood-gas shifts towards hypoxia and hypercapnia not only have an influence on the described immediate, psychological and physiological reactions on a macroscopic and microscopic level, but additionally on gene expression and metabolism on a molecular cellular level in many different body cells. Through this, the drastic disruptive intervention of masks in the physiology of the body also becomes clear down to the cellular level, e.g., in the activation of hypoxia-induced factor (HIF) through both hypercapnia and hypoxia-like effects [160]. HIF is a transcription factor that regulates cellular oxygen supply and activates signaling pathways relevant to adaptive responses. e.g., HIF inhibits stem cells, promotes tumor cell growth and inflammatory processes [160]. Based on the hypoxia- and hypercapnia-promoting effects of masks, which have been comprehensively described for the first time in our study, potential disruptive influences down to the intracellular level (HIF-a) can be assumed, especially through the prolonged and excessive use of masks. Thus, in addition to the vegetative chronic stress reaction in mask wearers, which is channeled via brain centers, there is also likely to be an adverse influence on metabolism at the cellular level. With the prospect of continued mask use in everyday life, this also opens up an interesting field of research for the future.

The fact that prolonged exposure to latently elevated CO_2 levels and unfavorable breathing air compositions has disease-promoting effects was recognized early on. As early as 1983, the WHO described "Sick Building Syndrome" (SBS) as a condition in which people living indoors experienced acute disease-relevant effects that increased with time of their stay, without specific causes or diseases [161,162]. The syndrome affects people who spend most of their time indoors, often with subliminally elevated CO_2 levels, and are prone to symptoms such as increased heart rate, rise in blood pressure, headaches, fatigue and difficulty concentrating [38,162]. Some of the complaints described in the mask studies we found (Figure 2) are surprisingly similar to those of Sick Building Syndrome [161]. Temperature, carbon dioxide content of the air, headaches, dizziness, drowsiness and itching also play a role in Sick Building Syndrome. On the one hand, masks could themselves be responsible for effects such as those described for Sick Building Syndrome when used for a longer period of time. On the other hand, they could additionally intensify these effects when worn in air-conditioned buildings, especially when masks are mandatory indoors. Nevertheless, there was a tendency towards higher systolic blood pressure values in mask wearers in some studies [21,31,34], but statistical significance was only found in two studies [25,35]. However, we found more relevant and significant evidence of heart

rate increase, headache, fatigue and concentration problems associated with mask wearers (Figure 2) indicating the clinical relevance of wearing masks.

According to the scientific results and findings, masks have measurably harmful effects not only on healthy people, but also on sick people and their relevance is likely to increase with the duration of use [69]. Further research is needed here to shed light on the long-term consequences of widespread mask use with subthreshold hypoxia and hypercapnia in the general population, also regarding possible exacerbating effects on cardiorespiratory lifestyle diseases such as hypertension, sleep apnea and metabolic syndrome. The already often elevated blood carbon dioxide (CO_2) levels in overweight people, sleep apnea patients and patients with overlap-COPD could possibly increase even further with everyday masks. Not only a high body mass index (BMI) but also sleep apnea are associated with hypercapnia during the day in these patients (even without masks) [19,163]. For such patients, hypercapnia means an increase in the risk of serious diseases with increased morbidity, which could then be further increased by excessive mask use [18,38].

The hypercapnia-induced effects of sympathetic stress activation are even cycle phase-dependent in women. Controlled by a progesterone mechanism, the sympathetic reaction, measured by increased blood pressure in the luteal phase, is considerably stronger [164]. This may also result in different sensitivities for healthy and sick women to undesirable effects masks have, which are related to an increase in carbon dioxide (CO_2).

In our review, negative physical and psychological changes caused by masks could be objectified even in younger and healthy individuals.

The physical and chemical parameters did not exceed the normal values in most cases but were statistically significantly measurable ($p < 0.05$) tending towards pathological ranges. They were accompanied by physical impairments (see Figure 2). It is well known that subthreshold stimuli are capable of causing pathological changes when exposed to them for a long time: not only a single high dose of a disturbance, but also a chronically persistent, subthreshold exposure to it often leads to illness [38,46–48,50–54]. The scientifically repeatedly measurable physical and chemical mask effects were often accompanied by typical subjective complaints and pathophysiological phenomena. The fact that these frequently occur simultaneously and together indicates a syndrome under masks.

Figure 2 sums up the significant mask-dependent physiological, psychological, somatic and general pathological changes and their frequent occurrence together is striking. Within the framework of the quantitative evaluation of the experimental studies, we were actually able to prove a statistically significant correlation of the observed side effects of fatigue and oxygen depletion under mask use with $p < 0.05$. In addition, we found a frequent, simultaneous and joint occurrence of further undesirable effects in the scientific studies (Figure 2). Statistically significant associations of such co-occurring, adverse effects have already been described in primary studies [21,29]. We detected a combined occurrence of the physical parameter temperature rise under the mask with the symptom respiratory impairment in seven of the nine studies concerned (88%). We found a similar result for the decrease in oxygen saturation under mask and the symptom respiratory impairment with a simultaneous detection in six of the eight studies concerned (67%). We detected a combined occurrence of carbon dioxide rise under N95 mask use in nine of the 11 scientific papers (82%). We found a similar result for oxygen drop under N95 mask use with simultaneous co-occurrence in eight of 11 primary papers (72%). The use of N95 masks was also associated with headache in six of the 10 primary studies concerned (60%). A combined occurrence of the physical parameters temperature rise and humidity under masks was even found 100% within six of the six studies with significant measurements of these parameters (Figure 2).

Since the symptoms were described in combination in mask wearers and were not observed in isolation in the majority of cases, we refer to them as general Mask-Induced Exhaustion Syndrome (MIES) because of the consistent presentation in numerous papers from different disciplines. These include the following, predominantly statistically significantly

($p < 0.05$) proven pathophysiological changes and subjective complaints, which often occur in combination as described above (see also Section 3.1 to Section 3.11, Figures 2–4):

- Increase in dead space volume [22,24,58,59] (Figure 3, Sections 3.1 and 3.2).
- Increase in breathing resistance [31,35,61,118] (Figure 3, Figure 2: Column 8).
- Increase in blood carbon dioxide [13,15,19,21–28] (Figure 2: Column 5).
- Decrease in blood oxygen saturation [18,19,21,23,28–34] (Figure 2: Column 4).
- Increase in heart rate [15,19,23,29,30,35] (Figure 2: Column 12).
- Decrease in cardiopulmonary capacity [31] (Section 3.2).
- Feeling of exhaustion [15,19,21,29,31–35,69] (Figure 2: Column 14).
- Increase in respiratory rate [15,21,23,34] (Figure 2: Column 9).
- Difficulty breathing and shortness of breath [15,19,21,23,25,29,31,34,35,71,85,101,133] (Figure 2: Column 13).
- Headache [19,27,37,66–68,83] (Figure 2: Column 17).
- Dizziness [23,29] (Figure 2: Column 16).
- Feeling of dampness and heat [15,16,22,29,31,35,85,133] (Figure 2: Column 7).
- Drowsiness (qualitative neurological deficits) [19,29,32,36,37] (Figure 2: Column 15).
- Decrease in empathy perception [99] (Figure 2: Column 19).
- Impaired skin barrier function with acne, itching and skin lesions [37,72,73] (Figure 2: Column 20–22).

It can be deduced from the results that the effects described in healthy people are all more pronounced in sick people, since their compensatory mechanisms, depending on the severity of the illness, are reduced or even exhausted. Some existing studies on and with patients with measurable pathological effects of the masks support this assumption [19,23,25,34]. In most scientific studies, the exposure time to masks in the context of the measurements/investigations was significantly less (in relation to the total wearing and duration of use) than is expected of the general public under the current pandemic regulations and ordinances.

The exposure time limits are little observed or knowingly disregarded in many areas today as already mentioned in Section 3.11 on occupational medicine. The above facts allow the conclusion that the described negative effects of masks, especially in some of our patients and the very elderly, may well be more severe and adverse with prolonged use than presented in some mask studies.

From a doctor's viewpoint, it may also be difficult to advise children and adults who, due to social pressure (to wear a mask) and the desire to feel they belong, suppress their own needs and concerns until the effects of masks have a noticeable negative impact on their health [76]. Nevertheless, the use of masks should be stopped immediately at the latest when shortness of breath, dizziness or vertigo occur [23,25]. From this aspect, it seems sensible for decision makers and authorities to provide information, to define instruction obligations and offer appropriate training for employers, teachers and other persons who have a supervisory or caregiving duty. Knowledge about first aid measures could also be refreshed and expanded accordingly in this regard.

Elderly, high-risk patients with lung disease, cardiac patients, pregnant women or stroke patients are advised to consult a physician to discuss the safety of an N95 mask as their lung volume or cardiopulmonary performance may be reduced [23]. A correlation between age and the occurrence of the aforementioned symptoms while wearing a mask has been statistically proven [19]. Patients with reduced cardiopulmonary function are at increased risk of developing serious respiratory failure with mask use according to the referenced literature [34]. Without the possibility of continuous medical monitoring, it can be concluded that they should not wear masks without close monitoring. The American Asthma and Allergy Society has already advised caution in the use of masks with regard to the COVID-19 pandemic for people with moderate and severe lung disease [165]. Since the severely overweight, sleep apnea patients and overlap-COPD sufferers are known to be prone to hypercapnia, they also represent a risk group for serious adverse health effects under extensive mask use [163]. This is because the potential of masks to produce additional

CO_2 retention may not only have a disruptive effect on the blood gases and respiratory physiology of sufferers, but may also lead to further serious adverse health effects in the long term. Interestingly, in an animal experiment an increase in CO_2 with hypercapnia leads to contraction of smooth airway muscles with constriction of bronchi [166]. This effect could explain the observed pulmonary decompensations of patients with lung disease under masks (Section 3.2) [23,34].

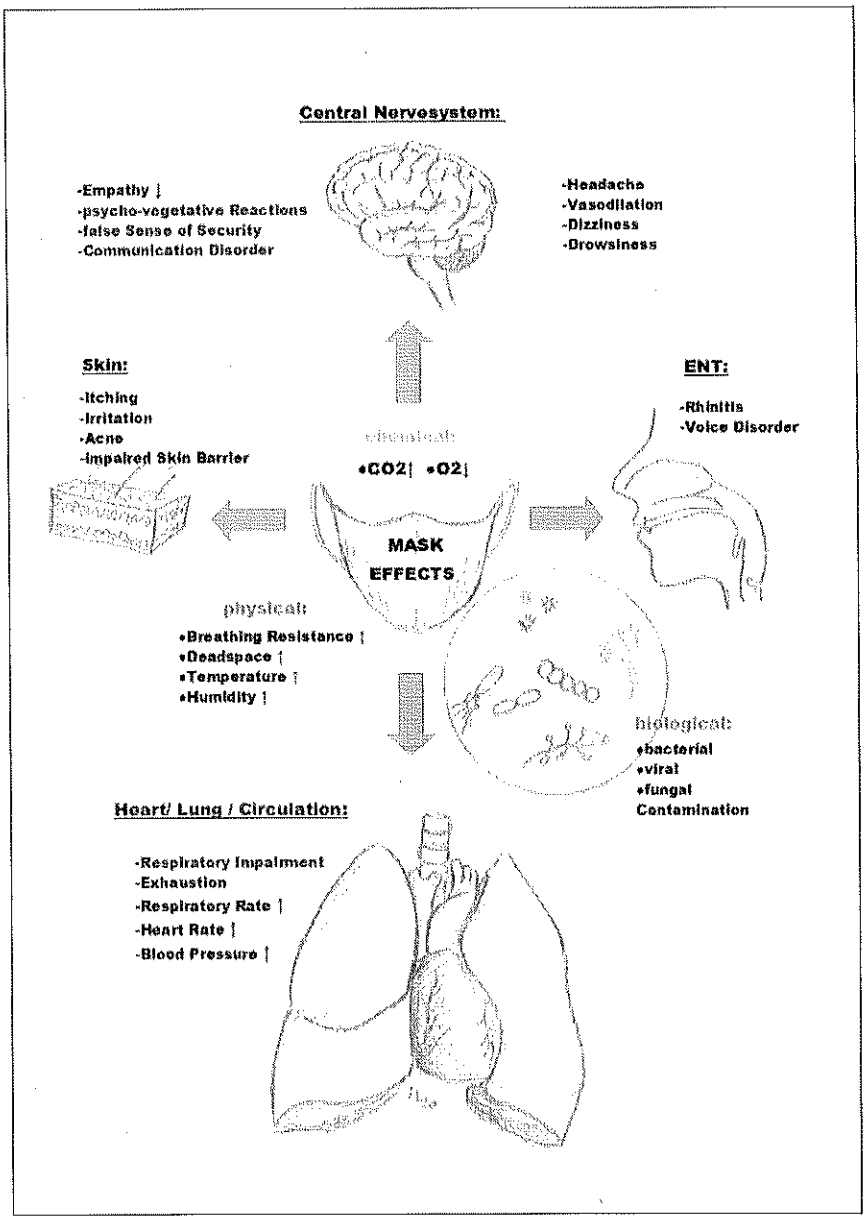

Figure 4. Unfavorable mask effects as components of Mask-Induced Exhaustion Syndrome (MIES). The chemical, physical and biological effects, as well as the organ system consequences mentioned, are all documented with statistically significant results in the scientific literature found (Figure 2). The term drowsiness is used here to summarize any qualitative neurological deficits described in the examined scientific literature.

Patients with renal insufficiency requiring dialysis are, according to the literature available, further candidates for a possible exemption from the mask requirement [34].

According to the criteria of the Centers for Disease Control and Prevention, GA, USA (CDC), sick and helpless people who cannot remove a mask on their own should be exempted from the mask requirement [82].

Since it can be assumed that children react even more sensitively to masks, the literature suggests that masks are a contraindication for children with epilepsies (hyperventilation as a trigger for seizures) [63]. In the field of pediatrics, special attention should also be paid to the mask symptoms described under psychological, psychiatric and sociological effects with possible triggering of panic attacks by CO_2 rebreathing in the case of predisposition and also reinforcement of claustrophobic fears [77–79,167]. The mask-related disturbance of verbal [43,45,71] and non-verbal communication and, thus, of social interaction is particularly serious for children. Masks restrict social interaction and block positive perceptions (smiling and laughing) and emotional mimicry [42]. The proven mask-induced mild to moderate cognitive impairment with impaired thinking, decreased attention and dizziness [19,23,29,32,36,37,39–41,69], as well as the psychological and neurological effects [135], should be additionally taken into account when masks are compulsory at school and in the vicinity of both public and non-public transport, also regarding the possibility of an increased risk of accidents (see also occupational health side effects and hazards) [19,29,32,36,37]. The exclusion criteria mentioned in pediatric studies on masks (see pediatric impairments, Section 3.14) [26,133] should also apply to an exclusion of these children from the general mask obligation in accordance with the scientific findings for the protection of the sick children concerned. The long-term sociological, psychological and educational consequences of a comprehensive masking requirement extended to schools are also unpredictable with regard to the psychological and physical development of healthy children [42,135]. Interestingly, according to the Corona Thesis Paper of the University of Bremen children "are infected less often, they become ill less often, the lethality is close to zero, and they also pass on the infection less often", according to the Thesis Paper 2.0 of the German University of Bremen on page 6 [138]. Studies conducted under real-life conditions with outcome endpoints showing hardly any infections, hardly any morbidity, hardly any mortality and only low contagiousness in children are clearly in the majority, according to Thesis Paper 3.0 of the German University of Bremen [138]. A recent German observational study (5600 reporting pediatricians) also showed a surprisingly low incidence of COVID-19 disease in children [168]. The infection of adults with SARS-CoV-2 by children has been considered in only one suspected case, but could not be proven with certainty, since the parents also had numerous contacts and exposure factors for viral infections due to their occupation. In this case, the circulating headlines in the public media that children contribute more to the incidence of infection are to be regarded as anecdotal.

In pregnant women, the use of masks during exertion or at rest over long periods of time is to be regarded as critical as little research has been done on this [20]. If there is clear scientific evidence of increased dead space ventilation with possible accumulation of CO_2 in the mother's blood, the use of masks by pregnant women for more than 1 h, as well as under physical stress, should be avoided in order to protect the unborn child [20,22]. The hypercapnia-promoting masks could act as a confounder of the fetal/maternal CO_2 gradient in this case (Section 3.6) [20,22,28].

According to the literature cited in the Section 3.5 on psychiatric side effects (personality disorders with anxiety and panic attacks, claustrophobia, dementia and schizophrenia), masking should only be done, if at all, with careful consideration of the advantages and disadvantages. Attention should be paid to possible provocation of the number and severity of panic attacks [77–79].

In patients with headaches, a worsening of symptoms can be expected with prolonged mask use (see also Section 3.3., neurological side effects) [27,66–68]. As a result of the increase in blood carbon dioxide (CO_2) when the mask is used, vasodilatation occurs in the central nervous system and the pulsation of the blood vessels decreases [27]. In this connection, it is also interesting to note radiological experiments that demonstrate an increase in brain volume under subthreshold, but still within normal limits of CO_2 increase

in the blood by means of structural MRI. The blood carbon dioxide increase was produced in seven subjects via rebreathing with resulting median carbon dioxide concentration of 42 mmHg and an interquartile range of 39.44 mmHg, corresponding to only a subthreshold increase given the normal values of 32–45 mmHg. In the experiment, there was a significant increase in brain parenchymal volume measurable under increased arterial CO_2 levels ($p < 0.02$), with a concomitant decrease in CSF spaces ($p < 0.04$), entirely in accordance with the Monroe–Kelly doctrine, according to which the total volume within the skull always remains the same. The authors interpreted the increase in brain volume as an expression of an increase in blood volume due to a CO_2 increase-induced dilation of the cerebral vessels [169]. The consequences of such equally subthreshold carbon dioxide (CO_2) increases even under masks [13,15,18,19,22,23,25] are unclear for people with pathological changes inside the skull (aneurysms, tumors, etc.) with associated vascular changes [27] and brain volume shifts [169] especially due to longer exposure while wearing a mask, but could be of great relevance due to the blood gas-related volume shifts that take place.

In view of the increased dead space volume, the long-term and increased accumulation and rebreathing of other respiratory air components apart from CO_2 is also unexplained, both in children and in old and sick people. Exhaled air contains over 250 substances, including irritant or toxic gases such as nitrogen oxides (NO), hydrogen sulfide (H2S), isoprene and acetone [170]. For nitrogen oxides [47] and hydrogen sulfide [46], pathological effects relevant to disease have been described in environmental medicine even at a low but chronic exposure [46–48]. Among the volatile organic compounds in exhaled air, acetone and isoprene dominate in terms of quantity, but allyl methyl sulfide, propionic acid and ethanol (some of bacterial origin) should also be mentioned [171]. Whether such substances also react chemically with each other underneath masks and in the dead space volume created by masks (Figure 3), and with the mask tissue itself, and in what quantities these and possible reaction products are rebreathed, has not yet been clarified. In addition to the blood gas changes described above (O_2 drop and CO_2 rise), these effects could also play a role with regard to undesirable mask effects. Further research is needed here and is of particular interest in the case of prolonged and ubiquitous use of masks.

The WHO sees the integration of individual companies and communities that produce their own fabric masks as a potential social and economic benefit. Due to the global shortage of surgical masks and personal protective equipment, it sees this as a source of income and points out that the reuse of fabric masks can reduce costs and waste and contribute to sustainability [2]. In addition to the question of certification procedures for such fabric masks, it should also be mentioned that due to the extensive mask obligation, textile (artificial) substances in the form of micro- and nanoparticles, some of which cannot be degraded in the body, are chronically absorbed into the body through inhalation to an unusual extent. In the case of medical masks, disposable polymers such as polypropylene, polyurethane, polyacrylonitrile, polystyrene, polycarbonate, polyethylene and polyester should be mentioned [140]. ENT physicians have already been able to detect such particles in the nasal mucosa of mask wearers with mucosal reactions in the sense of a foreign body reaction with rhinitis [96]. In the case of community masks, other substances from the textile industry are likely to be added to those mentioned above. The body will try to absorb these substances through macrophages and scavenger cells in the respiratory tract and alveoli as part of a foreign body reaction, whereby toxin release and corresponding local and generalized reactions may occur in an unsuccessful attempt to break them down [172]. Extensive respiratory protection in permanent long-term use (24/7), at least from a theoretical point of view, also potentially carries the risk of leading to a mask-related pulmonary [47] or even generalized disorder, as is already known from textile workers chronically exposed to organic dusts in the Third World (byssinosis) [172].

For the general public, from a scientific angle, it is necessary to draw on the long-standing knowledge of respiratory protection in occupational medicine in order to protect children in particular from harm caused by uncertified masks and improper use.

The universal undefined and extended mask requirement—without taking into account multiple predispositions and susceptibilities—contradicts the claim of an increasingly important individualized medicine with a focus on the unique characteristics of each individual [173].

A systematic review on the topic of masks is necessary according to the results of our scoping review. The primary studies often showed weaknesses in operationalization, especially in the evaluation of cognitive and neuropsychological parameters. Computerized test procedures will be useful here in the future. Mask research should also set itself the future goal of investigating and defining subgroups for whom respiratory protection use is particularly risky.

5. Limitations

Our approach with a focus on negative effects is in line with Villalonga-Olives and Kawachi [12]. With the help of such selective questioning in the sense of dialectics, new insights can be gained that might otherwise have remained hidden. Our literature search focused on adverse negative effects of masks, in particular to point out risks especially for certain patient groups. Therefore, publications presenting only positive effects of masks. were not considered in this review.

For a compilation of studies with harmless results when using masks, reference must, therefore, be made to reviews with a different research objective, whereby attention must be paid to possible conflicts of interest there. Some of the studies excluded by us lacking negative effects have shown methodological weaknesses (small, non-uniform experimental groups, missing control group even without masks due to corona constraints, etc.) [174]. In other words, if no negative concomitant effects were described in publications, it does not necessarily mean that masks have exclusively positive effects. It is quite possible that negative effects were simply not mentioned in the literature and the number of negative effects may well be higher than our review suggests.

We only searched one database, so the number of papers on negative mask effects may be higher than we reported.

In order to be able to describe characteristic effects for each mask type even more extensively, we did not have enough scientific data on the respective special designs of the masks. There is still a great need for research in this area due to the current pandemic situation with extensive mandatory masking.

In addition, the experiments evaluated in this paper do not always have uniform measurement parameters and study variables and, depending on the study, take into account the effect of masks at rest or under stress with subjects having different health conditions. Figure 2, therefore, represents a compromise. The results of the primary studies on mask use partially showed no natural variation in parameters, but often showed such clear correlations between symptoms and physiological changes, so that a statistical correlation analysis was not always necessary. We found a statistically significant correlation of oxygen deprivation and fatigue in 58% of the studies ($p < 0.05$). A statistically significant correlation evidence for other parameters has been previously demonstrated in primary studies [21,29].

The most commonly used personal particulate matter protective equipment in the COVID-19 pandemic is the N95 mask [23]. Due to its characteristics (better filtering function, but greater airway resistance and more dead space volume than other masks), the N95 mask is able to highlight negative effects of such protective equipment more clearly than others (Figure 3). Therefore, a relatively frequent consideration and evaluation of N95 masks within the studies found (30 of the 44 quantitatively evaluated studies, 68%) is even advantageous within the framework of our research question. Nevertheless, it remains to be noted that the community masks sold on the market are increasingly similar to the protective equipment that has been better investigated in scientific studies, such as surgical masks and N95 masks, since numerous manufacturers and users of community masks are striving to approximate the professional standard (surgical mask, N95/FFP2). Recent

study results on community masks indicate similar effects for respiratory physiology as described for medical masks: in a recent publication, fabric masks (community masks) also provoked a measurable increase in carbon dioxide $PtcCO_2$ in wearers during exertion and came very close to surgical masks in this effect [21].

Most of the studies cited in our paper included only short observation and application periods (mask-wearing durations investigated ranged from 5 min [26] to 12 h [19]. In only one study, a maximum observation period of an estimated 2-month period was chosen [37]. Therefore, the actual negative effects of masks over a longer application period might be more pronounced than presented in our work.

6. Conclusions

On the one hand, the advocacy of an extended mask requirement remains predominantly theoretical and can only be sustained with individual case reports, plausibility arguments based on model calculations and promising in vitro laboratory tests. Moreover, recent studies on SARS-CoV-2 show both a significantly lower infectivity [175] and a significantly lower case mortality than previously assumed, as it could be calculated that the median corrected infection fatality rate (IFR) was 0.10% in locations with a lower than average global COVID-19 population mortality rate [176]. In early October 2020, the WHO also publicly announced that projections show COVID-19 to be fatal for approximately 0.14% of those who become ill—compared to 0.10% for endemic influenza—again a figure far lower than expected [177].

On the other hand, the side effects of masks are clinically relevant.

In our work, we focused exclusively on the undesirable and negative side effects that can be produced by masks. Valid significant evidence of combined mask-related changes were objectified ($p < 0.05$, $n \geq 50\%$), and we found a clustered and common occurrence of the different adverse effects within the respective studies with significantly measured effects (Figure 2). We were able to demonstrate a statistically significant correlation of the observed adverse effect of hypoxia and the symptom of fatigue with $p < 0.05$ in the quantitative evaluation of the primary studies. Our review of the literature shows that both healthy and sick people can experience Mask-Induced Exhaustion Syndrome (MIES), with typical changes and symptoms that are often observed in combination, such as an increase in breathing dead space volume [22,24,58,59], increase in breathing resistance [31,35,60,61], increase in blood carbon dioxide [13,15,17,19,21–30,35], decrease in blood oxygen saturation [18,19,21,23,28–34], increase in heart rate [23,29,30,35], increase in blood pressure [25,35], decrease in cardiopulmonary capacity [31], increase in respiratory rate [15,21,23,34,36], shortness of breath and difficulty breathing [15,17,19,21,23,25,29,31,34,35,60,71,85,101,133], headache [19,27,29,37,66–68,71,83], dizziness [23,29], feeling hot and clammy [17,22,29,31,35,44,71,85,133], decreased ability to concentrate [29], decreased ability to think [36,37], drowsiness [19,29,32,36,37], decrease in empathy perception [99], impaired skin barrier function [37,72,73] with itching [31,35,67,71–73,91–93], acne, skin lesions and irritation [37,72,73], overall perceived fatigue and exhaustion [15,19,21,29,31,32,34,35,69] (Figures 2–4).

Wearing masks does not consistently cause clinical deviations from the norm of physiological parameters, but according to the scientific literature, a long-term pathological consequence with clinical relevance is to be expected owing to a longer-lasting effect with a subliminal impact and significant shift in the pathological direction. For changes that do not exceed normal values, but are persistently recurring, such as an increase in blood carbon dioxide [38,160], an increase in heart rate [55] or an increase in respiratory rate [56,57], which have been documented while wearing a mask [13,15,17,19,21–30,34,35] (Figure 2), a long-term generation of high blood pressure [25,35], arteriosclerosis and coronary heart disease and of neurological diseases is scientifically obvious [38,55–57,160]. This pathogenetic damage principle with a chronic low-dose exposure with long-term effect, which leads to disease or disease-relevant conditions, has already been extensively studied and described in many areas of environmental medicine [38,46–54]. Extended

mask-wearing would have the potential, according to the facts and correlations we have found, to cause a chronic sympathetic stress response induced by blood gas modifications and controlled by brain centers. This in turn induces and triggers immune suppression and metabolic syndrome with cardiovascular and neurological diseases.

We not only found evidence in the reviewed mask literature of potential long-term effects, but also evidence of an increase in direct short-term effects with increased mask-wearing time in terms of cumulative effects for: carbon dioxide retention, drowsiness, headache, feeling of exhaustion, skin irritation (redness, itching) and microbiological contamination (germ colonization) [19,22,37,66,68,69,89,91,92].

Overall, the exact frequency of the described symptom constellation MIES in the mask-using populace remains unclear and cannot be estimated due to insufficient data.

Theoretically, the mask-induced effects of the drop in blood gas oxygen and increase in carbon dioxide extend to the cellular level with induction of the transcription factor HIF (hypoxia-induced factor) and increased inflammatory and cancer-promoting effects [160] and can, thus, also have a negative influence on pre-existing clinical pictures.

In any case, the MIES potentially triggered by masks (Figures 3 and 4) contrasts with the WHO definition of health: "health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." [178].

All the scientific facts found in our work expand the knowledge base for a differentiated view of the mask debate. This gain can be relevant for decision makers who have to deal with the issue of mandatory mask use during the pandemic under constant review of proportionality as well as for physicians who can advise their patients more appropriately on this basis. For certain diseases, taking into account the literature found in this study, it is also necessary for the attending physician to weigh up the benefits and risks with regard to a mask obligation. With an overall strictly scientific consideration, a recommendation for mask exemption can become justifiable within the framework of a medical appraisal (Figure 5).

Increased risk of adverse effects when using masks:

Internal diseases
COPD
Sleep Apnea Syndrome
advanced renal Failure
Obesity
Cardiopulmonary Dysfunction
Asthma

Psychiatric Illness
Claustrophobia
Panic Disorder
Personality Disorders
Dementia
Schizophrenia
helpless Patients
fixed and sedated Patients

Neurological Diseases
Migraines and Headache Sufferers
Patients with intracranial Masses
Epilepsy

Pediatric Diseases
Asthma
Respiratory diseases
Cardiopulmonary Diseases
Neuromuscular Diseases
Epilepsy

ENT Diseases
Vocal Cord Disorders
Rhinitis and obstructive Diseases

Dermatological Diseases
Acne
Atopic

Occupational Health Restrictions
moderate / heavy physical Work

Gynecological restrictions
Pregnant Women

Figure 5. Diseases/predispositions with significant risks, according to the literature found, when using masks. Indications for weighing up medical mask exemption certificates.

In addition to protecting the health of their patients, doctors should also base their actions on the guiding principle of the 1948 Geneva Declaration, as revised in 2017. According to this, every doctor vows to put the health and dignity of his patient first and, even under threat, not to use his medical knowledge to violate human rights and civil liberties [9]. Within the framework of these findings, we, therefore, propagate an explicitly medically judicious, legally compliant action in consideration of scientific factual reality [2,4,5,16,130,132,143,175–177] against a predominantly assumption-led claim to a general effectiveness of masks, always taking into account possible unwanted individual ef-

fects for the patient and mask wearer concerned, entirely in accordance with the principles of evidence-based medicine and the ethical guidelines of a physician.

The results of the present literature review could help to include mask-wearing in the differential diagnostic pathophysiological cause consideration of every physician when corresponding symptoms are present (MIES, Figure 4). In this way, the physician can draw on an initial complaints catalogue that may be associated with mask-wearing (Figure 2) and also exclude certain diseases from the general mask requirement (Figure 5).

For scientists, the prospect of continued mask use in everyday life suggests areas for further research. In our view, further research is particularly desirable in the gynecological (fetal and embryonic) and pediatric fields, as children are a vulnerable group that would face the longest and, thus, most profound consequences of a potentially risky mask use. Basic research at the cellular level regarding mask-induced triggering of the transcription factor HIF with potential promotion of immunosuppression and carcinogenicity also appears to be useful under this circumstance. Our scoping review shows the need for a systematic review.

The described mask-related changes in respiratory physiology can have an adverse effect on the wearer's blood gases sub-clinically and in some cases also clinically manifest and, therefore, have a negative effect on the basis of all aerobic life, external and internal respiration, with an influence on a wide variety of organ systems and metabolic processes with physical, psychological and social consequences for the individual human being.

Author Contributions: Conceptualization, K.K. and O.H.; methodology, K.K. and O.H.; software, O.H.; formal analysis, K.K., O.H., P.G., A.P., B.K., D.G., S.F. and O.K.; investigation, K.K., O.H., P.G., A.P., B.K., D.G., S.F. and O.K.; writing—original draft preparation, K.K., O.H., P.G., A.P., B.K., D.G., S.F. and O.K.; writing—review and editing K.K., O.H., P.G., A.P., B.K., D.G., S.F. and O.K. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: We thank Bonita Blankart, for translation of the manuscript. For support in their special field we wish to thank: Tanja Boehnke (Psychology), Nicola Fels (Pediatrics), Michael Grönke (Anesthesiology), Basile Marcos (Psychiatry), Bartholomeus Maris (Gynecology) and Markus Veit (Pharmacist).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. World Health Organization. *WHO-Advice on the Use of Masks in the Context of COVID-19: Interim Guidance, 6 April 2020*; World Health Organization: Geneva, Switzerland, 2020; Available online: https://apps.who.int/iris/handle/10665/331693 (accessed on 7 November 2020).
2. World Health Organization. *WHO-Advice on the Use of Masks in the Context of COVID-19: Interim Guidance, 5 June 2020*; World Health Organization: Geneva, Switzerland, 2020; Available online: https://apps.who.int/iris/handle/10665/332293 (accessed on 7 November 2020).
3. Chu, D.K.; Akl, E.A.; Duda, S.; Solo, K.; Yaacoub, S.; Schünemann, H.J.; Chu, D.K.; Akl, E.A.; El-harakeh, A.; Bognanni, A.; et al. Physical Distancing, Face Masks, and Eye Protection to Prevent Person-to-Person Transmission of SARS-CoV-2 and COVID-19: A Systematic Review and Meta-Analysis. *Lancet* **2020**, *395*, 1973–1987. [CrossRef]
4. Jefferson, T.; Jones, M.; Ansari, L.A.A.; Bawazeer, G.; Beller, E.; Clark, J.; Conly, J.; Mar, C.D.; Dooley, E.; Ferroni, E.; et al. Physical Interventions to Interrupt or Reduce the Spread of Respiratory Viruses. Part 1-Face Masks, Eye Protection and Person Distancing: Systematic Review and Meta-Analysis. *medRxiv* **2020**. [CrossRef]
5. Kappstein, I. Mund-Nasen-Schutz in der Öffentlichkeit: Keine Hinweise für eine Wirksamkeit. *Krankenh. Up2date* **2020**, *15*, 279–295. [CrossRef]
6. De Brouwer, C. Wearing a Mask, a Universal Solution against COVID-19 or an Additional Health Risk? 2020. Available online: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3676885 (accessed on 12 November 2020). [CrossRef]
7. Ewig, S.; Gatermann, S.; Lemmen, S. Die Maskierte Gesellschaft. *Pneumologie* **2020**, *74*, 405–408. [CrossRef] [PubMed]

8. Great Barrington Declaration Great Barrington Declaration and Petition. Available online: https://gbdeclaration.org/ (accessed on 9 November 2020).
9. WMA-The World Medical Association-WMA Declaration of Geneva. Available online: https://www.wma.net/policies-post/wma-declaration-of-geneva/ (accessed on 7 November 2020).
10. WMA-The World Medical Association-WMA Declaration of Helsinki–Ethical Principles for Medical Research Involving Human Subjects. Available online: https://www.wma.net/policies-post/wma-declaration-of-geneva/ (accessed on 7 November 2020).
11. WMA-The World Medical Association-WMA Declaration of Lisbon on the Rights of the Patient. Available online: https://www.wma.net/policies-post/wma-declaration-of-lisbon-on-the-rights-of-the-patient/ (accessed on 7 November 2020).
12. Villalonga-Olives, E.; Kawachi, I. The Dark Side of Social Capital: A Systematic Review of the Negative Health Effects of Social Capital. *Soc. Sci. Med.* **2017**, *194*, 105–127. [CrossRef]
13. Butz, U. Rückatmung von Kohlendioxid bei Verwendung von Operationsmasken als hygienischer Mundschutz an medizinischem Fachpersonal. Ph.D. Thesis, Fakultät für Medizin der Technischen Universität München, Munich, Germany, 2005.
14. Smolka, L.; Borkowski, J.; Zaton, M. The Effect of Additional Dead Space on Respiratory Exchange Ratio and Carbon Dioxide Production Due to Training. *J. Sports Sci. Med.* **2014**, *13*, 36–43. [PubMed]
15. Roberge, R.J.; Kim, J.-H.; Benson, S.M. Absence of Consequential Changes in Physiological, Thermal and Subjective Responses from Wearing a Surgical Mask. *Respir. Physiol. Neurobiol.* **2012**, *181*, 29–35. [CrossRef] [PubMed]
16. Matuschek, C.; Moll, F.; Fangerau, H.; Fischer, J.C.; Zänker, K.; van Griensven, M.; Schneider, M.; Kindgen-Milles, D.; Knoefel, W.T.; Lichtenberg, A.; et al. Face Masks: Benefits and Risks during the COVID-19 Crisis. *Eur. J. Med. Res.* **2020**, *25*, 32. [CrossRef]
17. Roberge, R.J.; Coca, A.; Williams, W.J.; Powell, J.B.; Palmiero, A.J. Physiological Impact of the N95 Filtering Facepiece Respirator on Healthcare Workers. *Respir. Care* **2010**, *55*, 569–577.
18. Pifarré, F.; Zabala, D.D.; Grazioli, G.; de Yzaguirre i Maura, I. COVID 19 and Mask in Sports. *Apunt. Sports Med.* **2020**. [CrossRef]
19. Rebmann, T.; Carrico, R.; Wang, J. Physiologic and Other Effects and Compliance with Long-Term Respirator Use among Medical Intensive Care Unit Nurses. *Am. J. Infect. Control* **2013**, *41*, 1218–1223. [CrossRef]
20. Roeckner, J.T.; Krstić, N.; Sipe, B.H.; Običan, S.G. N95 Filtering Facepiece Respirator Use during Pregnancy: A Systematic Review. *Am. J. Perinatol.* **2020**, *37*, 995–1001. [CrossRef]
21. Georgi, C.; Haase-Fielitz, A.; Meretz, D.; Gäsert, L.; Butter, C. Einfluss gängiger Gesichtsmasken auf physiologische Parameter und Belastungsempfinden unter arbeitstypischer körperlicher Anstrengung. *Deutsches Ärzteblatt* **2020**, 674–675. [CrossRef]
22. Roberge, R.J.; Kim, J.-H.; Powell, J.B. N95 Respirator Use during Advanced Pregnancy. *Am. J. Infect. Control* **2014**, *42*, 1097–1100. [CrossRef]
23. Kyung, S.Y.; Kim, Y.; Hwang, H.; Park, J.-W.; Jeong, S.H. Risks of N95 Face Mask Use in Subjects with COPD. *Respir. Care* **2020**, *65*, 658–664. [CrossRef]
24. Epstein, D.; Korytny, A.; Isenberg, Y.; Marcusohn, E.; Zukermann, R.; Bishop, B.; Minha, S.; Raz, A.; Miller, A. Return to Training in the COVID-19 Era: The Physiological Effects of Face Masks during Exercise. *Scand. J. Med. Sci. Sports* **2020**. [CrossRef]
25. Mo, Y.; Wei, D.; Mai, Q.; Chen, C.; Yu, H.; Jiang, C.; Tan, X. Risk and Impact of Using Mask on COPD Patients with Acute Exacerbation during the COVID-19 Outbreak: A Retrospective Study. *Res. Sq.* **2020**. [CrossRef]
26. Goh, D.Y.T.; Mun, M.W.; Lee, W.L.J.; Teoh, O.H.; Rajgor, D.D. A Randomised Clinical Trial to Evaluate the Safety, Fit, Comfort of a Novel N95 Mask in Children. *Sci. Rep.* **2019**, *9*, 18952. [CrossRef]
27. Bharatendu, C.; Ong, J.J.Y.; Goh, Y.; Tan, B.Y.Q.; Chan, A.C.Y.; Tang, J.Z.Y.; Leow, A.S.; Chin, A.; Sooi, K.W.X.; Tan, Y.L.; et al. Powered Air Purifying Respirator (PAPR) Restores the N95 Face Mask Induced Cerebral Hemodynamic Alterations among Healthcare Workers during COVID-19 Outbreak. *J. Neurol. Sci.* **2020**, *417*, 117078. [CrossRef]
28. Tong, P.S.Y.; Kale, A.S.; Ng, K.; Loke, A.P.; Choolani, M.A.; Lim, C.L.; Chan, Y.H.; Chong, Y.S.; Tambyah, P.A.; Yong, E.-L. Respiratory Consequences of N95-Type Mask Usage in Pregnant Healthcare Workers—A Controlled Clinical Study. *Antimicrob. Resist. Infect. Control* **2015**, *4*, 48. [CrossRef]
29. Liu, C.; Li, G.; He, Y.; Zhang, Z.; Ding, Y. Effects of Wearing Masks on Human Health and Comfort during the COVID-19 Pandemic. *IOP Conf. Ser. Earth Environ. Sci.* **2020**, *531*, 012034. [CrossRef]
30. Beder, A.; Büyükkoçak, U.; Sabuncuoğlu, H.; Keskil, Z.A.; Keskil, S. Preliminary Report on Surgical Mask Induced Deoxygenation during Major Surgery. *Neurocirugía* **2008**, *19*, 121–126. [CrossRef]
31. Fikenzer, S.; Uhe, T.; Lavall, D.; Rudolph, U.; Falz, R.; Busse, M.; Hepp, P.; Laufs, U. Effects of Surgical and FFP2/N95 Face Masks on Cardiopulmonary Exercise Capacity. *Clin. Res. Cardiol.* **2020**, *109*, 1522–1530. [CrossRef] [PubMed]
32. Jagim, A.R.; Dominy, T.A.; Camic, C.L.; Wright, G.; Doberstein, S.; Jones, M.T.; Oliver, J.M. Acute Effects of the Elevation Training Mask on Strength Performance in Recreational Weight Lifters. *J. Strength Cond. Res.* **2018**, *32*, 482–489. [CrossRef]
33. Porcari, J.P.; Probst, L.; Forrester, K.; Doberstein, S.; Foster, C.; Cress, M.L.; Schmidt, K. Effect of Wearing the Elevation Training Mask on Aerobic Capacity, Lung Function, and Hematological Variables. *J. Sports Sci. Med.* **2016**, *15*, 379–386.
34. Kao, T.-W.; Huang, K.-C.; Huang, Y.-L.; Tsai, T.-J.; Hsieh, B.-S.; Wu, M.-S. The Physiological Impact of Wearing an N95 Mask during Hemodialysis as a Precaution against SARS in Patients with End-Stage Renal Disease. *J. Formos. Med. Assoc.* **2004**, *103*, 624–628.
35. Li, Y.; Tokura, H.; Guo, Y.P.; Wong, A.S.W.; Wong, T.; Chung, J.; Newton, E. Effects of Wearing N95 and Surgical Facemasks on Heart Rate, Thermal Stress and Subjective Sensations. *Int. Arch. Occup. Environ. Health* **2005**, *78*, 501–509. [CrossRef]
36. Johnson, A.T. Respirator Masks Protect Health but Impact Performance: A Review. *J. Biol. Eng.* **2016**, *10*, 4. [CrossRef]

37. Rosner, E. Adverse Effects of Prolonged Mask Use among Healthcare Professionals during COVID-19. *J. Infect. Dis. Epidemiol.* **2020**. [CrossRef]
38. Azuma, K.; Kagi, N.; Yanagi, U.; Osawa, H. Effects of Low-Level Inhalation Exposure to Carbon Dioxide in Indoor Environments: A Short Review on Human Health and Psychomotor Performance. *Environ. Int.* **2018**, *121*, 51–56. [CrossRef]
39. Drechsler, M.; Morris, J. Carbon Dioxide Narcosis. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2020.
40. Noble, J.; Jones, J.G.; Davis, E.J. Cognitive Function during Moderate Hypoxaemia. *Anaesth. Intensive Care* **1993**, *21*, 180–184. [CrossRef]
41. Fothergill, D.M.; Hedges, D.; Morrison, J.B. Effects of CO_2 and N_2 Partial Pressures on Cognitive and Psychomotor Performance. *Undersea Biomed. Res.* **1991**, *18*, 1–19.
42. Spitzer, M. Masked Education? The Benefits and Burdens of Wearing Face Masks in Schools during the Current Corona Pandemic. *Trends Neurosci. Educ.* **2020**, *20*, 100138. [CrossRef]
43. Heider, C.A.; Álvarez, M.L.; Fuentes-López, E.; González, C.A.; León, N.I.; Verástegui, D.C.; Badía, P.I.; Napolitano, C.A. Prevalence of Voice Disorders in Healthcare Workers in the Universal Masking COVID-19 Era. *Laryngoscope* **2020**. [CrossRef]
44. Roberge, R.J.; Kim, J.-H.; Coca, A. Protective Facemask Impact on Human Thermoregulation: An Overview. *Ann. Occup. Hyg.* **2012**, *56*, 102–112. [CrossRef]
45. Palmiero, A.J.; Symons, D.; Morgan, J.W.; Shaffer, R.E. Speech Intelligelibility Assessment of Protective Facemasks and Air-Purifying Respirators. *J. Occup. Environ. Hyg.* **2016**, *13*, 960–968. [CrossRef]
46. Simonton, D.; Spears, M. Human Health Effects from Exposure to Low-Level Concentrations of Hydrogen Sulfide. *Occup. Health Saf. (Waco Tex.)* **2007**, *76*, 102–104.
47. Salimi, F.; Morgan, G.; Rolfe, M.; Samoli, E.; Cowie, C.T.; Hanigan, I.; Knibbs, L.; Cope, M.; Johnston, F.H.; Guo, Y.; et al. Long-Term Exposure to Low Concentrations of Air Pollutants and Hospitalisation for Respiratory Diseases: A Prospective Cohort Study in Australia. *Environ. Int.* **2018**, *121*, 415–420. [CrossRef]
48. Dominici, F.; Schwartz, J.; Di, Q.; Braun, D.; Choirat, C.; Zanobetti, A. *Assessing Adverse Health Effects of Long-Term Exposure to Low Levels of Ambient Air Pollution: Phase 1 Research Report*; Health Effects Institute: Boston, MA, USA, 2019; pp. 1–51.
49. Alleva, R.; Manzella, N.; Gaetani, S.; Bacchetti, T.; Bracci, M.; Ciarapica, V.; Monaco, F.; Borghi, B.; Amati, M.; Ferretti, G.; et al. Mechanism Underlying the Effect of Long-Term Exposure to Low Dose of Pesticides on DNA Integrity. *Environ. Toxicol.* **2018**, *33*, 476–487. [CrossRef]
50. Roh, T.; Lynch, C.F.; Weyer, P.; Wang, K.; Kelly, K.M.; Ludewig, G. Low-Level Arsenic Exposure from Drinking Water Is Associated with Prostate Cancer in Iowa. *Environ. Res.* **2017**, *159*, 338–343. [CrossRef]
51. Deering, K.E.; Callan, A.C.; Prince, R.L.; Lim, W.H.; Thompson, P.L.; Lewis, J.R.; Hinwood, A.L.; Devine, A. Low-Level Cadmium Exposure and Cardiovascular Outcomes in Elderly Australian Women: A Cohort Study. *Int. J. Hyg. Environ. Health* **2018**, *221*, 347–354. [CrossRef] [PubMed]
52. Kosnett, M. Health Effects of Low Dose Lead Exposure in Adults and Children, and Preventable Risk Posed by the Consumption of Game Meat Harvested with Lead Ammunition. In *Ingestion of Lead from Spent Ammunition: Implications for Wildlife and Humans*; The Peregrine Fund: Boise, ID, USA, 2009. [CrossRef]
53. Crinnion, W.J. Environmental Medicine, Part Three: Long-Term Effects of Chronic Low-Dose Mercury Exposure. *Altern. Med. Rev.* **2000**, *5*, 209–223. [PubMed]
54. Wu, S.; Han, J.; Vleugels, R.A.; Puett, R.; Laden, F.; Hunter, D.J.; Qureshi, A.A. Cumulative Ultraviolet Radiation Flux in Adulthood and Risk of Incident Skin Cancers in Women. *Br. J. Cancer* **2014**, *110*, 1855–1861. [CrossRef] [PubMed]
55. Custodis, F.; Schirmer, S.H.; Baumhäkel, M.; Heusch, G.; Böhm, M.; Laufs, U. Vascular Pathophysiology in Response to Increased Heart Rate. *J. Am. Coll. Cardiol.* **2010**, *56*, 1973–1983. [CrossRef]
56. Russo, M.A.; Santarelli, D.M.; O'Rourke, D. The Physiological Effects of Slow Breathing in the Healthy Human. *Breathe* **2017**, *13*, 298–309. [CrossRef]
57. Nuckowska, M.K.; Gruszecki, M.; Kot, J.; Wolf, J.; Guminski, W.; Frydrychowski, A.F.; Wtorek, J.; Narkiewicz, K.; Winklewski, P.J. Impact of Slow Breathing on the Blood Pressure and Subarachnoid Space Width Oscillations in Humans. *Sci. Rep.* **2019**, *9*, 6232. [CrossRef]
58. Johnson, A.T.; Scott, W.H.; Lausted, C.G.; Coyne, K.M.; Sahota, M.S.; Johnson, M.M. Effect of External Dead Volume on Performance While Wearing a Respirator. *AIHAJ-Am. Ind. Hyg. Assoc.* **2000**, *61*, 678–684. [CrossRef]
59. Xu, M.; Lei, Z.; Yang, J. Estimating the Dead Space Volume between a Headform and N95 Filtering Facepiece Respirator Using Microsoft Kinect. *J. Occup. Environ. Hyg.* **2015**, *12*, 538–546. [CrossRef]
60. Lee, H.P.; Wang, D.Y. Objective Assessment of Increase in Breathing Resistance of N95 Respirators on Human Subjects. *Ann. Occup. Hyg.* **2011**, *55*, 917–921. [CrossRef]
61. Roberge, R.; Bayer, E.; Powell, J.; Coca, A.; Roberge, M.; Benson, S. Effect of Exhaled Moisture on Breathing Resistance of N95 Filtering Facepiece Respirators. *Ann. Occup. Hyg.* **2010**, *54*, 671–677. [CrossRef]
62. Jamjoom, A.; Nikkar-Esfahani, A.; Fitzgerald, J. Operating Theatre Related Syncope in Medical Students: A Cross Sectional Study. *BMC Med. Educ.* **2009**, *9*, 14. [CrossRef]
63. Asadi-Pooya, A.A.; Cross, J.H. Is Wearing a Face Mask Safe for People with Epilepsy? *Acta Neurol. Scand.* **2020**, *142*, 314–316. [CrossRef]

64. Lazzarino, A.I.; Steptoe, A.; Hamer, M.; Michie, S. Covid-19: Important Potential Side Effects of Wearing Face Masks That We Should Bear in Mind. *BMJ* **2020**, *369*, m2003. [CrossRef]
65. Guaranha, M.S.B.; Garzon, E.; Buchpiguel, C.A.; Tazima, S.; Yacubian, E.M.T.; Sakamoto, A.C. Hyperventilation Revisited: Physiological Effects and Efficacy on Focal Seizure Activation in the Era of Video-EEG Monitoring. *Epilepsia* **2005**, *46*, 69–75. [CrossRef]
66. Ong, J.J.Y.; Bharatendu, C.; Goh, Y.; Tang, J.Z.Y.; Sooi, K.W.X.; Tan, Y.L.; Tan, B.Y.Q.; Teoh, H.-L.; Ong, S.T.; Allen, D.M.; et al. Headaches Associated With Personal Protective Equipment-A Cross-Sectional Study among Frontline Healthcare Workers During COVID-19. *Headache* **2020**, *60*, 864–877. [CrossRef]
67. Jacobs, J.L.; Ohde, S.; Takahashi, O.; Tokuda, Y.; Omata, F.; Fukui, T. Use of Surgical Face Masks to Reduce the Incidence of the Common Cold among Health Care Workers in Japan: A Randomized Controlled Trial. *Am. J. Infect. Control* **2009**, *37*, 417–419. [CrossRef]
68. Ramirez-Moreno, J.M. Mask-Associated de Novo Headache in Healthcare Workers during the Covid-19 Pandemic. *medRxiv* **2020**. [CrossRef]
69. Shenal, B.V.; Radonovich, L.J.; Cheng, J.; Hodgson, M.; Bender, B.S. Discomfort and Exertion Associated with Prolonged Wear of Respiratory Protection in a Health Care Setting. *J. Occup. Environ. Hyg.* **2011**, *9*, 59–64. [CrossRef]
70. Rains, S.A. The Nature of Psychological Reactance Revisited: A Meta-Analytic Review. *Hum. Commun. Res.* **2013**, *39*, 47–73. [CrossRef]
71. Matusiak, Ł.; Szepietowska, M.; Krajewski, P.; Białynicki-Birula, R.; Szepietowski, J.C. Inconveniences Due to the Use of Face Masks during the COVID-19 Pandemic: A Survey Study of 876 Young People. *Dermatol. Ther.* **2020**, *33*, e13567. [CrossRef]
72. Foo, C.C.I.; Goon, A.T.J.; Leow, Y.; Goh, C. Adverse Skin Reactions to Personal Protective Equipment against Severe Acute Respiratory Syndrome–a Descriptive Study in Singapore. *Contact Dermat.* **2006**, *55*, 291–294. [CrossRef]
73. Hua, W.; Zuo, Y.; Wan, R.; Xiong, L.; Tang, J.; Zou, L.; Shu, X.; Li, L. Short-Term Skin Reactions Following Use of N95 Respirators and Medical Masks. *Contact Dermat.* **2020**, *83*, 115–121. [CrossRef]
74. Prousa, D. Studie zu psychischen und psychovegetativen Beschwerden mit den aktuellen Mund-Nasenschutz-Verordnungen. *PsychArchives* **2020**. [CrossRef]
75. Sell, T.K.; Hosangadi, D.; Trotochaud, M. Misinformation and the US Ebola Communication Crisis: Analyzing the Veracity and Content of Social Media Messages Related to a Fear-Inducing Infectious Disease Outbreak. *BMC Public Health* **2020**, *20*, 550. [CrossRef]
76. Ryan, R.M.; Deci, E.L. Self-determination theory and the role of basic psychological needs in personality and the organization of behavior. In *Handbook of Personality: Theory and Research*, 3rd ed.; The Guilford Press: New York, NY, USA, 2008; pp. 654–678. ISBN 978-1-59385-836-0.
77. Kent, J.M.; Papp, L.A.; Martinez, J.M.; Browne, S.T.; Coplan, J.D.; Klein, D.F.; Gorman, J.M. Specificity of Panic Response to CO(2) Inhalation in Panic Disorder: A Comparison with Major Depression and Premenstrual Dysphoric Disorder. *Am. J. Psychiatry* **2001**, *158*, 58–67. [CrossRef] [PubMed]
78. Morris, L.S.; McCall, J.G.; Charney, D.S.; Murrough, J.W. The Role of the Locus Coeruleus in the Generation of Pathological Anxiety. *Brain Neurosci. Adv.* **2020**, *4*. [CrossRef] [PubMed]
79. Gorman, J.M.; Askanazi, J.; Liebowitz, M.R.; Fyer, A.J.; Stein, J.; Kinney, J.M.; Klein, D.F. Response to Hyperventilation in a Group of Patients with Panic Disorder. *Am. J. Psychiatry* **1984**, *141*, 857–861. [CrossRef] [PubMed]
80. Tsugawa, A.; Sakurai, S.; Inagawa, Y.; Hirose, D.; Kaneko, Y.; Ogawa, Y.; Serisawa, S.; Takenoshita, N.; Sakurai, H.; Kanetaka, H.; et al. Awareness of the COVID-19 Outbreak and Resultant Depressive Tendencies in Patients with Severe Alzheimer's Disease. *JAD* **2020**, *77*, 539–541. [CrossRef]
81. Maguire, P.A.; Reay, R.E.; Looi, J.C. Nothing to Sneeze at-Uptake of Protective Measures against an Influenza Pandemic by People with Schizophrenia: Willingness and Perceived Barriers. *Australas. Psychiatry* **2019**, *27*, 171–178. [CrossRef]
82. COVID-19: Considerations for Wearing Masks | CDC. Available online: https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/cloth-face-cover-guidance.html (accessed on 12 November 2020).
83. Lim, E.C.H.; Seet, R.C.S.; Lee, K.-H.; Wilder-Smith, E.P.V.; Chuah, B.Y.S.; Ong, B.K.C. Headaches and the N95 Face-mask amongst Healthcare Providers. *Acta Neurol. Scand.* **2006**, *113*, 199–202. [CrossRef]
84. Badri, F.M.A. Surgical Mask Contact Dermatitis and Epidemiology of Contact Dermatitis in Healthcare Workers. *Curr. Allergy Clin. Immunol.* **2017**, *30*, 183–188.
85. Scarano, A.; Inchingolo, F.; Lorusso, F. Facial Skin Temperature and Discomfort When Wearing Protective Face Masks: Thermal Infrared Imaging Evaluation and Hands Moving the Mask. *Int. J. Environ. Res. Public Health* **2020**, *17*, 4624. [CrossRef]
86. Luksamijarulkul, P.; Aiempradit, N.; Vatanasomboon, P. Microbial Contamination on Used Surgical Masks among Hospital Personnel and Microbial Air Quality in Their Working Wards: A Hospital in Bangkok. *Oman Med. J.* **2014**, *29*, 346–350. [CrossRef]
87. Chughtai, A.A.; Stelzer-Braid, S.; Rawlinson, W.; Pontivivo, G.; Wang, Q.; Pan, Y.; Zhang, D.; Zhang, Y.; Li, L.; MacIntyre, C.R. Contamination by Respiratory Viruses on Outer Surface of Medical Masks Used by Hospital Healthcare Workers. *BMC Infect. Dis.* **2019**, *19*, 491. [CrossRef]
88. Monalisa, A.C.; Padma, K.B.; Manjunath, K.; Hemavathy, E.; Varsha, D. Microbial Contamination of the Mouth Masks Used by Post-Graduate Students in a Private Dental Institution: An In-Vitro Study. *IOSR J. Dent. Med. Sci.* **2017**, *16*, 61–67.
89. Liu, Z.; Chang, Y.; Chu, W.; Yan, M.; Mao, Y.; Zhu, Z.; Wu, H.; Zhao, J.; Dai, K.; Li, H.; et al. Surgical Masks as Source of Bacterial Contamination during Operative Procedures. *J. Orthop. Transl.* **2018**, *14*, 57–62. [CrossRef]

90. Robert Koch-Institut. *Influenza-Monatsbericht*; Robert Koch-Institut: Berlin, Germany, 2020.
91. Techasatian, L.; Lebsing, S.; Uppala, R.; Thaowandee, W.; Chaiyarit, J.; Supakunpinyo, C.; Panombualert, S.; Mairiang, D.; Saengnipanthkul, S.; Wichajarn, K.; et al. The Effects of the Face Mask on the Skin Underneath: A Prospective Survey During the COVID-19 Pandemic. *J. Prim. Care Community Health* **2020**, *11*, 2150132720966167. [CrossRef]
92. Lan, J.; Song, Z.; Miao, X.; Li, H.; Li, Y.; Dong, L.; Yang, J.; An, X.; Zhang, Y.; Yang, L.; et al. Skin Damage among Health Care Workers Managing Coronavirus Disease-2019. *J. Am. Acad. Dermatol.* **2020**, *82*, 1215–1216. [CrossRef]
93. Szepietowski, J.C.; Matusiak, Ł.; Szepietowska, M.; Krajewski, P.K.; Białynicki-Birula, R. Face Mask-Induced Itch: A Self-Questionnaire Study of 2,315 Responders during the COVID-19 Pandemic. *Acta Derm.-Venereol.* **2020**, *100*, adv00152. [CrossRef]
94. Darlenski, R.; Tsankov, N. COVID-19 Pandemic and the Skin: What Should Dermatologists Know? *Clin. Dermatol.* **2020**. [CrossRef]
95. Muley, P.; 'Mask Mouth'-a Novel Threat to Oral Health in the COVID Era–Dr Pooja Muley. Dental Tribune South Asia 2020. Available online: https://in.dental-tribune.com/news/mask-mouth-a-novel-threat-to-oral-health-in-the-covid-era/ (accessed on 12 November 2020).
96. Klimek, L.; Huppertz, T.; Alali, A.; Spielhaupter, M.; Hörmann, K.; Matthias, C.; Hagemann, J. A New Form of Irritant Rhinitis to Filtering Facepiece Particle (FFP) Masks (FFP2/N95/KN95 Respirators) during COVID-19 Pandemic. *World Allergy Organ. J.* **2020**, *13*, 100474. [CrossRef]
97. COVID-19 Mythbusters–World Health Organization. Available online: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public/myth-busters (accessed on 28 January 2021).
98. Asadi, S.; Cappa, C.D.; Barreda, S.; Wexler, A.S.; Bouvier, N.M.; Ristenpart, W.D. Efficacy of Masks and Face Coverings in Controlling Outward Aerosol Particle Emission from Expiratory Activities. *Sci. Rep.* **2020**, *10*, 15665. [CrossRef]
99. Wong, C.K.M.; Yip, B.H.K.; Mercer, S.; Griffiths, S.; Kung, K.; Wong, M.C.; Chor, J.; Wong, S.Y. Effect of Facemasks on Empathy and Relational Continuity: A Randomised Controlled Trial in Primary Care. *BMC Fam. Pract.* **2013**, *14*, 200. [CrossRef]
100. World Health Organization; United Nations Children's Fund. *WHO-Advice on the Use of Masks for Children in the Community in the Context of COVID-19: Annex to the Advice on the Use of Masks in the Context of COVID-19, 21 August 2020*; World Health Organization: Geneva, Switzerland, 2020.
101. Person, E.; Lemercier, C.; Royer, A.; Reychler, G. Effet du port d'un masque de soins lors d'un test de marche de six minutes chez des sujets sains. *Rev. Mal. Respir.* **2018**, *35*, 264–268. [CrossRef]
102. Johnson, A.T.; Scott, W.H.; Phelps, S.J.; Caretti, D.M.; Koh, F.C. How Is Respirator Comfort Affected by Respiratory Resistance? *J. Int. Soc. Respir. Prot.* **2005**, *22*, 38.
103. Koh, F.C.; Johnson, A.T.; Scott, W.H.; Phelps, S.J.; Francis, E.B.; Cattungal, S. The Correlation between Personality Type and Performance Time While Wearing a Respirator. *J. Occup. Environ. Hyg.* **2006**, *3*, 317–322. [CrossRef]
104. Deutsche Gesetzliche Unfallversicherung. *DGUV Grundsätze für Arbeitsmedizinische Vorsorgeuntersuchungen*; Alfons, W., Ed.; Gentner Verlag: Stuttgart, Germany, 2010; ISBN 978-3-87247-733-0.
105. Browse by Country-NATLEX. Available online: https://www.ilo.org/dyn/natlex/natlex4.byCountry?p_lang=en (accessed on 28 January 2021).
106. BAuA-SARS-CoV-2 FAQ Und Weitere Informationen-Kennzeichnung von Masken Aus USA, Kanada, Australien/Neuseeland, Japan, China Und Korea-Bundesanstalt Für Arbeitsschutz Und Arbeitsmedizin. Available online: https://www.baua.de/DE/Themen/Arbeitsgestaltung-im-Betrieb/Coronavirus/pdf/Kennzeichnung-Masken.html (accessed on 28 January 2021).
107. Veit, M. Hauptsache Maske!? *DAZ.Online*. 2020, p. S26. Available online: https://www.deutsche-apotheker-zeitung.de/daz-az/2020/daz-33-2020/hauptsache-maske (accessed on 12 November 2020).
108. MacIntyre, C.R.; Seale, H.; Dung, T.C.; Hien, N.T.; Nga, P.T.; Chughtai, A.A.; Rahman, B.; Dwyer, D.E.; Wang, Q. A Cluster Randomised Trial of Cloth Masks Compared with Medical Masks in Healthcare Workers. *BMJ Open* **2015**, *5*, e006577. [CrossRef]
109. MacIntyre, C.R.; Chughtai, A.A. Facemasks for the Prevention of Infection in Healthcare and Community Settings. *BMJ* **2015**, *350*, h694. [CrossRef]
110. MacIntyre, C.R.; Wang, Q.; Seale, H.; Yang, P.; Shi, W.; Gao, Z.; Rahman, B.; Zhang, Y.; Wang, X.; Newall, A.T.; et al. A Randomized Clinical Trial of Three Options for N95 Respirators and Medical Masks in Health Workers. *Am. J. Respir. Crit. Care Med.* **2013**, *187*, 960–966. [CrossRef]
111. Dellweg, D.; Lepper, P.M.; Nowak, D.; Köhnlein, T.; Olgemöller, U.; Pfeifer, M. Position Paper of the German Respiratory Society (DGP) on the Impact of Community Masks on Self-Protection and Protection of Others in Regard to Aerogen Transmitted Diseases. *Pneumologie* **2020**, *74*, 331–336. [CrossRef]
112. Luckman, A.; Zeitoun, H.; Isoni, A.; Loomes, G.; Vlaev, I.; Powdthavee, N.; Read, D. Risk Compensation during COVID-19: The Impact of Face Mask Usage on Social Distancing. *OSF Preprints*. 2020. Available online: https://osf.io/rb8he/ (accessed on 25 October 2020).
113. Sharma, I.; Vashnav, M.; Sharma, R. COVID-19 Pandemic Hype: Losers and Gainers. *Indian J. Psychiatry* **2020**, *62*, S420–S430. [CrossRef] [PubMed]
114. BfArM-Empfehlungen Des BfArM-Hinweise Des BfArM Zur Verwendung von Mund–Nasen-Bedeckungen (z.B. Selbst Hergestellten Masken, "Community-Oder DIY-Masken"), Medizinischen Gesichtsmasken Sowie Partikelfiltrierenden Halbmasken (FFP1, FFP2 Und FFP3) Im Zusammenhang Mit Dem Coronavirus (SARS-CoV-2/Covid-19). Available online: https://www.bfarm.de/SharedDocs/Risikoinformationen/Medizinprodukte/DE/schutzmasken.html (accessed on 12 November 2020).

115. MacIntyre, C.R.; Wang, Q.; Cauchemez, S.; Seale, H.; Dwyer, D.E.; Yang, P.; Shi, W.; Gao, Z.; Pang, X.; Zhang, Y.; et al. A Cluster Randomized Clinical Trial Comparing Fit-Tested and Non-Fit-Tested N95 Respirators to Medical Masks to Prevent Respiratory Virus Infection in Health Care Workers. *Influenza Other Respir. Viruses* **2011**, *5*, 170–179. [CrossRef] [PubMed]
116. Gralton, J.; McLaws, M.-L. Protecting Healthcare Workers from Pandemic Influenza: N95 or Surgical Masks? *Crit. Care Med.* **2010**, *38*, 657–667. [CrossRef] [PubMed]
117. Smith, J.D.; MacDougall, C.C.; Johnstone, J.; Copes, R.A.; Schwartz, B.; Garber, G.E. Effectiveness of N95 Respirators versus Surgical Masks in Protecting Health Care Workers from Acute Respiratory Infection: A Systematic Review and Meta-Analysis. *CMAJ* **2016**, *188*, 567–574. [CrossRef] [PubMed]
118. Lee, S.-A.; Grinshpun, S.A.; Reponen, T. Respiratory Performance Offered by N95 Respirators and Surgical Masks: Human Subject Evaluation with NaCl Aerosol Representing Bacterial and Viral Particle Size Range. *Ann. Occup. Hyg.* **2008**, *52*, 177–185. [CrossRef] [PubMed]
119. Zhu, N.; Zhang, D.; Wang, W.; Li, X.; Yang, B.; Song, J.; Zhao, X.; Huang, B.; Shi, W.; Lu, R.; et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N. Engl. J. Med.* **2020**. [CrossRef]
120. Oberg, T.; Brosseau, L.M. Surgical Mask Filter and Fit Performance. *Am. J. Infect. Control* **2008**, *36*, 276–282. [CrossRef]
121. Eninger, R.M.; Honda, T.; Adhikari, A.; Heinonen-Tanski, H.; Reponen, T.; Grinshpun, S.A. Filter Performance of N99 and N95 Facepiece Respirators Against Viruses and Ultrafine Particles. *Ann. Occup. Hyg.* **2008**, *52*, 385–396. [CrossRef]
122. Morawska, L. Droplet Fate in Indoor Environments, or Can We Prevent the Spread of Infection? *Indoor Air* **2006**, *16*, 335–347. [CrossRef]
123. Ueki, H.; Furusawa, Y.; Iwatsuki-Horimoto, K.; Imai, M.; Kabata, H.; Nishimura, H.; Kawaoka, Y. Effectiveness of Face Masks in Preventing Airborne Transmission of SARS-CoV-2. *mSphere* **2020**, *5*, e00637-20. [CrossRef]
124. Radonovich, L.J.; Simberkoff, M.S.; Bessesen, M.T.; Brown, A.C.; Cummings, D.A.T.; Gaydos, C.A.; Los, J.G.; Krosche, A.E.; Gibert, C.L.; Gorse, G.J.; et al. N95 Respirators vs Medical Masks for Preventing Influenza Among Health Care Personnel: A Randomized Clinical Trial. *JAMA* **2019**, *322*, 824–833. [CrossRef]
125. Loeb, M.; Dafoe, N.; Mahony, J.; John, M.; Sarabia, A.; Glavin, V.; Webby, R.; Smieja, M.; Earn, D.J.D.; Chong, S.; et al. Surgical Mask vs N95 Respirator for Preventing Influenza Among Health Care Workers: A Randomized Trial. *JAMA* **2009**, *302*, 1865–1871. [CrossRef]
126. Konda, A.; Prakash, A.; Moss, G.A.; Schmoldt, M.; Grant, G.D.; Guha, S. Aerosol Filtration Efficiency of Common Fabrics Used in Respiratory Cloth Masks. *ACS Nano* **2020**, *14*, 6339–6347. [CrossRef]
127. Chughtai, A. Use of Cloth Masks in the Practice of Infection Control–Evidence and Policy Gaps. *Int. J. Infect. Control* **2013**, *9*. [CrossRef]
128. Labortest-Schutzmasken im Härtetest: Die Meisten Filtern Ungenügend. Available online: https://www.srf.ch/news/panorama/labortest-schutzmasken-im-haertetest-die-meisten-filtern-ungenuegend (accessed on 12 November 2020).
129. MacIntyre, C.R.; Cauchemez, S.; Dwyer, D.E.; Seale, H.; Cheung, P.; Browne, G.; Fasher, M.; Wood, J.; Gao, Z.; Booy, R.; et al. Face Mask Use and Control of Respiratory Virus Transmission in Households. *Emerg. Infect. Dis.* **2009**, *15*, 233–241. [CrossRef]
130. Xiao, J.; Shiu, E.Y.C.; Gao, H.; Wong, J.Y.; Fong, M.W.; Ryu, S.; Cowling, B.J. Nonpharmaceutical Measures for Pandemic Influenza in Nonhealthcare Settings—Personal Protective and Environmental Measures. *Emerg. Infect. Dis.* **2020**, *26*, 967–975. [CrossRef]
131. Aiello, A.E.; Murray, G.F.; Perez, V.; Coulborn, R.M.; Davis, B.M.; Uddin, M.; Shay, D.K.; Waterman, S.H.; Monto, A.S. Mask Use, Hand Hygiene, and Seasonal Influenza-like Illness among Young Adults: A Randomized Intervention Trial. *J. Infect. Dis.* **2010**, *201*, 491–498. [CrossRef]
132. Bundgaard, H.; Bundgaard, J.S.; Raaschou-Pedersen, D.E.T.; von Buchwald, C.; Todsen, T.; Norsk, J.B.; Pries-Heje, M.M.; Vissing, C.R.; Nielsen, P.B.; Winsløw, U.C.; et al. Effectiveness of Adding a Mask Recommendation to Other Public Health Measures to Prevent SARS-CoV-2 Infection in Danish Mask Wearers. *Ann. Intern. Med.* **2020**. [CrossRef]
133. Smart, N.R.; Horwell, C.J.; Smart, T.S.; Galea, K.S. Assessment of the Wearability of Facemasks against Air Pollution in Primary School-Aged Children in London. *Int. J. Environ. Res. Public Health* **2020**, *17*, 3935. [CrossRef]
134. Forgie, S.E.; Reitsma, J.; Spady, D.; Wright, B.; Stobart, K. The "Fear Factor" for Surgical Masks and Face Shields, as Perceived by Children and Their Parents. *Pediatrics* **2009**, *124*, e777–e781. [CrossRef]
135. Schwarz, S.; Jenetzky, E.; Krafft, H.; Maurer, T.; Martin, D. Corona Children Studies "Co-Ki": First Results of a Germany-Wide Registry on Mouth and Nose Covering (Mask) in Children. *Monatsschrift Kinderheilkde* **2021**, 1–10. [CrossRef]
136. Zoccal, D.B.; Furuya, W.I.; Bassi, M.; Colombari, D.S.A.; Colombari, E. The Nucleus of the Solitary Tract and the Coordination of Respiratory and Sympathetic Activities. *Front. Physiol.* **2014**, *5*, 238. [CrossRef]
137. Neilson, S. The Surgical Mask Is a Bad Fit for Risk Reduction. *CMAJ* **2016**, *188*, 606–607. [CrossRef]
138. SOCIUM Research Center on Inequality and Social Policy, Universität Bremen. Available online: https://www.socium.uni-bremen.de/ueber-das-socium/aktuelles/archiv/ (accessed on 28 January 2021).
139. Fadare, O.O.; Okoffo, E.D. Covid-19 Face Masks: A Potential Source of Microplastic Fibers in the Environment. *Sci. Total Environ.* **2020**, *737*, 140279. [CrossRef]
140. Potluri, P.; Needham, P. *Technical Textiles for Protection (Manchester EScholar-The University of Manchester)*; Woodhead Publishing: Cambridge, UK, 2005.
141. Schnurr, R.E.J.; Alboiu, V.; Chaudhary, M.; Corbett, R.A.; Quanz, M.E.; Sankar, K.; Srain, H.S.; Thavarajah, V.; Xanthos, D.; Walker, T.R. Reducing Marine Pollution from Single-Use Plastics (SUPs): A Review. *Mar. Pollut. Bull.* **2018**, *137*, 157–171. [CrossRef]

142. Reid, A.J.; Carlson, A.K.; Creed, I.F.; Eliason, E.J.; Gell, P.A.; Johnson, P.T.J.; Kidd, K.A.; MacCormack, T.J.; Olden, J.D.; Ormerod, S.J.; et al. Emerging Threats and Persistent Conservation Challenges for Freshwater Biodiversity. *Biol. Rev. Camb. Philos. Soc.* **2019**, *94*, 849–873. [CrossRef]
143. Fisher, K.A.; Tenforde, M.W.; Feldstein, L.R.; Lindsell, C.J.; Shapiro, N.I.; Files, D.C.; Gibbs, K.W.; Erickson, H.L.; Prekker, M.E.; Steingrub, J.S.; et al. Community and Close Contact Exposures Associated with COVID-19 among Symptomatic Adults ≥18 Years in 11 Outpatient Health Care Facilities-United States, July 2020. *MMWR Morb. Mortal. Wkly. Rep.* **2020**, *69*, 1258–1264. [CrossRef]
144. Belkin, N. The Evolution of the Surgical Mask: Filtering Efficiency versus Effectiveness. *Infect. Control Hosp. Epidemiol.* **1997**, *18*, 49–57. [CrossRef]
145. Cowling, B.J.; Chan, K.-H.; Fang, V.J.; Cheng, C.K.Y.; Fung, R.O.P.; Wai, W.; Sin, J.; Seto, W.H.; Yung, R.; Chu, D.W.S.; et al. Facemasks and Hand Hygiene to Prevent Influenza Transmission in Households: A Cluster Randomized Trial. *Ann. Intern. Med.* **2009**, *151*, 437–446. [CrossRef]
146. Cowling, B.J.; Zhou, Y.; Ip, D.K.M.; Leung, G.M.; Aiello, A.E. Face Masks to Prevent Transmission of Influenza Virus: A Systematic Review. *Epidemiol. Infect.* **2010**, *138*, 449–456. [CrossRef]
147. Institute of Medicine (US). Committee on Personal Protective Equipment for Healthcare Personnel to Prevent Transmission of Pandemic Influenza and Other Viral Respiratory Infections: Current Research Issues. In *Preventing Transmission of Pandemic Influenza and Other Viral Respiratory Diseases: Personal Protective Equipment for Healthcare Personnel: Update 2010*; Larson, E.L., Liverman, C.T., Eds.; National Academies Press (US): Washington, DC, USA, 2011; ISBN 978-0-309-16254-8.
148. Matuschek, C.; Moll, F.; Fangerau, H.; Fischer, J.C.; Zänker, K.; van Griensven, M.; Schneider, M.; Kindgen-Milles, D.; Knoefel, W.T.; Lichtenberg, A.; et al. The History and Value of Face Masks. *Eur. J. Med. Res.* **2020**, *25*, 23. [CrossRef] [PubMed]
149. Spooner, J.L. History of Surgical Face Masks. *AORN J.* **1967**, *5*, 76–80. [CrossRef]
150. Burgess, A.; Horii, M. Risk, Ritual and Health Responsibilisation: Japan's "safety Blanket" of Surgical Face Mask-Wearing. *Sociol. Health Illn.* **2012**, *34*, 1184–1198. [CrossRef] [PubMed]
151. Beck, U. *Risk Society, towards a New Modernity*; SAGE Publications Ltd: Thousand Oaks, CA, USA, 1992.
152. Cheng, K.K.; Lam, T.H.; Leung, C.C. Wearing Face Masks in the Community during the COVID-19 Pandemic: Altruism and Solidarity. *Lancet* **2020**. [CrossRef]
153. Melnychuk, M.C.; Dockree, P.M.; O'Connell, R.G.; Murphy, P.R.; Balsters, J.H.; Robertson, I.H. Coupling of Respiration and Attention via the Locus Coeruleus: Effects of Meditation and Pranayama. *Psychophysiology* **2018**, *55*, e13091. [CrossRef] [PubMed]
154. Andresen, M.C.; Kunze, D.L. Nucleus Tractus Solitarius–Gateway to Neural Circulatory Control. *Annu. Rev. Physiol.* **1994**, *56*, 93–116. [CrossRef] [PubMed]
155. Kline, D.D.; Ramirez-Navarro, A.; Kunze, D.L. Adaptive Depression in Synaptic Transmission in the Nucleus of the Solitary Tract after In Vivo Chronic Intermittent Hypoxia: Evidence for Homeostatic Plasticity. *J. Neurosci.* **2007**, *27*, 4663–4673. [CrossRef]
156. King, T.L.; Heesch, C.M.; Clark, C.G.; Kline, D.D.; Hasser, E.M. Hypoxia Activates Nucleus Tractus Solitarii Neurons Projecting to the Paraventricular Nucleus of the Hypothalamus. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2012**, *302*, R1219–R1232. [CrossRef]
157. Yackle, K.; Schwarz, L.A.; Kam, K.; Sorokin, J.M.; Huguenard, J.R.; Feldman, J.L.; Luo, L.; Krasnow, M.A. Breathing Control Center Neurons That Promote Arousal in Mice. *Science* **2017**, *355*, 1411–1415. [CrossRef]
158. Menuet, C.; Connelly, A.A.; Bassi, J.K.; Melo, M.R.; Le, S.; Kamar, J.; Kumar, N.N.; McDougall, S.J.; McMullan, S.; Allen, A.M. PreBötzinger Complex Neurons Drive Respiratory Modulation of Blood Pressure and Heart Rate. *eLife* **2020**, *9*, e57288. [CrossRef]
159. Zope, S.A.; Zope, R.A. Sudarshan Kriya Yoga: Breathing for Health. *Int. J. Yoga* **2013**, *6*, 4–10. [CrossRef]
160. Cummins, E.P.; Strowitzki, M.J.; Taylor, C.T. Mechanisms and Consequences of Oxygen and Carbon Dioxide Sensing in Mammals. *Physiol. Rev.* **2020**, *100*, 463–488. [CrossRef]
161. Jafari, M.J.; Khajevandi, A.A.; Mousavi Najarkola, S.A.; Yekaninejad, M.S.; Pourhoseingholi, M.A.; Omidi, L.; Kalantary, S. Association of Sick Building Syndrome with Indoor Air Parameters. *Tanaffos* **2015**, *14*, 55–62.
162. Redlich, C.A.; Sparer, J.; Cullen, M.R. Sick-Building Syndrome. *Lancet* **1997**, *349*, 1013–1016. [CrossRef]
163. Kaw, R.; Hernandez, A.V.; Walker, E.; Aboussouan, L.; Mokhlesi, B. Determinants of Hypercapnia in Obese Patients with Obstructive Sleep Apnea: A Systematic Review and Metaanalysis of Cohort Studies. *Chest* **2009**, *136*, 787–796. [CrossRef]
164. Edwards, N.; Wilcox, I.; Polo, O.J.; Sullivan, C.E. Hypercapnic Blood Pressure Response Is Greater during the Luteal Phase of the Menstrual Cycle. *J. Appl. Physiol.* **1996**, *81*, 2142–2146. [CrossRef]
165. AAFA Community Services. What People with Asthma Need to Know about Face Masks and Coverings during the COVID-19 Pandemic. Available online: https://community.aafa.org/blog/what-people-with-asthma-need-to-know-about-face-masks-and-coverings-during-the-covid-19-pandemic (accessed on 29 January 2021).
166. Shigemura, M.; Lecuona, E.; Angulo, M.; Homma, T.; Rodríguez, D.A.; Gonzalez-Gonzalez, F.J.; Welch, L.C.; Amarelle, L.; Kim, S.-J.; Kaminski, N.; et al. Hypercapnia Increases Airway Smooth Muscle Contractility via Caspase-7-Mediated MiR-133a-RhoA Signaling. *Sci. Transl. Med.* **2018**, *10*, eaat1662. [CrossRef]
167. Roberge, R. Facemask Use by Children during Infectious Disease Outbreaks. *Biosecur. Bioterror.* **2011**, *9*, 225–231. [CrossRef]
168. Schwarz, S.; Jenetzky, E.; Krafft, H.; Maurer, T.; Steuber, C.; Reckert, T.; Fischbach, T.; Martin, D. Corona bei Kindern: Die Co-Ki Studie. *Mon. Kinderheilkde* **2020**. [CrossRef]
169. van der Kleij, L.A.; De Vis, J.B.; de Bresser, J.; Hendrikse, J.; Siero, J.C.W. Arterial CO_2 Pressure Changes during Hypercapnia Are Associated with Changes in Brain Parenchymal Volume. *Eur. Radiol. Exp.* **2020**, *4*, 17. [CrossRef]

170. Geer Wallace, M.A.; Pleil, J.D. Evolution of Clinical and Environmental Health Applications of Exhaled Breath Research: Review of Methods: Instrumentation for Gas-Phase, Condensate, and Aerosols. *Anal. Chim. Acta* **2018**, *1024*, 18–38. [CrossRef] [PubMed]
171. Sukul, P.; Schubert, J.K.; Zanaty, K.; Trefz, P.; Sinha, A.; Kamysek, S.; Miekisch, W. Exhaled Breath Compositions under Varying Respiratory Rhythms Reflects Ventilatory Variations: Translating Breathomics towards Respiratory Medicine. *Sci. Rep.* **2020**, *10*, 14109. [CrossRef] [PubMed]
172. Lai, P.S.; Christiani, D.C. Long-Term Respiratory Health Effects in Textile Workers. *Curr. Opin. Pulm. Med.* **2013**, *19*, 152–157. [CrossRef] [PubMed]
173. Goetz, L.H.; Schork, N.J. Personalized Medicine: Motivation, Challenges and Progress. *Fertil. Steril.* **2018**, *109*, 952–963. [CrossRef]
174. Samannan, R.; Holt, G.; Calderon-Candelario, R.; Mirsaeidi, M.; Campos, M. Effect of Face Masks on Gas Exchange in Healthy Persons and Patients with COPD. *Ann. ATS* **2020**. [CrossRef]
175. Streeck, H.; Schulte, B.; Kuemmerer, B.; Richter, E.; Hoeller, T.; Fuhrmann, C.; Bartok, E.; Dolscheid, R.; Berger, M.; Wessendorf, L.; et al. Infection Fatality Rate of SARS-CoV-2 Infection in a German Community with a Super-Spreading Event. *medRxiv* **2020**. [CrossRef]
176. Ioannidis, J. The Infection Fatality Rate of COVID-19 Inferred from Seroprevalence Data. *medRxiv* **2020**. [CrossRef]
177. Executive Board: Special Session on the COVID-19 Response. Available online: https://www.who.int/news-room/events/detail/2020/10/05/default-calendar/executive-board-special-session-on-the-covid19-response (accessed on 13 November 2020).
178. International Health Conference. WHO-Constitution of the World Health Organization. 1946. *Bull. World Health Organ.* **2002**, *80*, 983–984.

Exhibit 9

Chambers Law Office

Richard C. Chambers, Jr.
Joseph Spinale
John P. Rauseo †
Janis Stanziani †
Matthew Littleton *

Paralegal *
Of Counsel †

Telephone: (781) 581-2031
Facsimile: (781) 581-8449

220 Broadway, Suite 404
Lynnfield, MA 01940

www.ChambersLawOffice.com

September 16, 2021

SENT VIA CERTIFIED MAIL 7017 1450 0000 1344 1835,
RETURN RECEIPT REQUESTED AND U.S. FIRST CLASS MAIL

The Wang Center for the Performing Arts, Inc.
(d/b/a Boch Center)
270 Tremont Street
Boston, MA 02116

RE: Mr. Michael Bush
280 Lowell Street
Carlisle MA 01741

To Whom It May Concern:

Please be advised that this office represents Mr. Michael Bush, (hereinafter "Bush"), who resides in Carlisle, Massachusetts. I am hereby making a formal demand on The Wang Center for the Performing Arts, Inc., d/b/a Boch Center, (hereinafter "Boch Center") for relief pertaining to the following. This letter is intended to serve as a Demand for relief in accordance with Massachusetts General Laws Chapter 93A.

It is my understanding that, using the hyperlinks in the Boch Center's promotional email messages to Bush, on July 25, 2021 Bush purchased tickets online to the *Cirque Dreams Holidaze* show to be held at your Boch Center Shubert Theatre on December 11, 2021; and on July 11, 2021 Bush purchased tickets, in good-faith, online to the *Il Divo "For Once In My Life"* Tour show to be held at your Boch Center Wang Theatre on September 3rd, 2021.

Bush contends that you failed to disclose, in your promotional emails and/or the online purchase process, to him that he would have to undergo vaccination(s), medical test(s) and/or wear a mask in order to attend the shows. Had such requirements been disclosed to Bush, he would not have purchased the tickets. Subsequent to his purchases, Bush received an email message informing him that the *Il Divo show* had been rescheduled to February 22nd, 2022.

On or about August 23rd, 2021 Bush received an email message from the Boch Center (enclosed hereto and incorporated herein as Exhibit 1 and hereinafter referred to as the "policy") informing him that starting September 14th, 2021 he and other guests at your theatres' shows

would have to wear mask(s) as well as be "fully vaccinated" or show a negative COVID test result to attend show(s) for which they had previously purchased tickets. 940 CMR 3.16 states, "an act or practice is a violation of M.G.L. c.93A, § 2 if: (1) It is oppressive or otherwise unconscionable in any respect; or (2) Any person or other legal entity subject to this act fails to disclose to a buyer or prospective buyer any fact, the disclosure of which may have influenced the buyer or prospective buyer not to enter into the transaction…"

We submit that the virus associated with the infectious disease COVID-19 SARS CoV 2 mutates readily, is airborne and highly transmissible, and has non-human animal reservoirs. Hence, similar to the annual influenza virus that has existed for over a century, the spread of SARS-CoV-2 and COVID-19 cannot be stopped. [i] Yet, your policy makes the deceptive claim that it is intended to "stop the spread" of COVID-19. Furthermore, by implementing such a policy, you have effectively assumed responsibility and liability for infections and resulting COVID-19 illnesses that persons may contract in your theatres.

Additionally, the "vaccines" currently with Emergency Use Authorization(s) or approval(s) from the U.S. Food and Drug Administration (FDA) for prevention of COVID-19 do not prevent infection or transmission of SARS-CoV-2 (the virus associated with COVID-19). [ii] Thus, your policy is deceptive by falsely representing that such vaccinations "stop the spread" of COVID-19.

Therefore, in compliance with Massachusetts General Laws Chapter 93A. I am specifying in detail the unfair and/or deceptive trade practices committed by the Boch Center, *See Accord, Mackenzie v. Auto Supermart, Inc.* 1988 Mass.App.Div. 5. *See also Spring v. Geriatric Auth.*, 394 Mass. 274, 475 N.E. 2d 727 (1985). These are as follows:

First, your policy unfairly discriminates against people with naturally acquired immunity to COVID-19. This is all the more unfair given that naturally acquired immunity has been shown to provide greater resistance to infection and disease and to be longer-lasting than immunity conferred by the so-called "vaccines" against SARS-CoV-2/COVID-19. [iii]

Second, the immunity conferred by the only "vaccine" currently approved against SARS-CoV-2 by the FDA is known to wane substantially within just a matter of months. Yet, despite that having been publicly known before you emailed your policy to Bush, your policy made no distinction between those customers who have been recently "vaccinated" and those who had been "vaccinated" many months before attending a show at one of your theatres.

Third, your policy mentions that a guest would either have to provide proof of being "fully vaccinated" or a negative result from a "COVID test" within 72 hours of the show. Yet, at the time you emailed your policy to Bush and to date, there were no tests for SARS-CoV-2 approved by the FDA. The only tests available have been issued Emergency Use Authorizations (EUA) by the FDA and such products are by their definition experimental or investigational in nature. Thus, your policy is deceptive by requiring tests that are not formally approved for the purpose your policy intends them to be used. Additionally, even if the negative test results that guests/customer provide were accurate at the time of testing, those guests/customers could become infected and carry a substantial viral load between the time they were tested and the time

they attend their shows at your theatres. Thus, your policy makes further deceptive claims by failing to acknowledge and disclose that medical fact.

Fourth, your policy **unfairly discriminates against people** for whom the "vaccines" currently authorized or approved for use against SARS-CoV-2 by the FDA are inappropriate for medical and/or religious reasons. It also unfairly discriminates against people for whom the "COVID tests" authorized by the FDA for investigational use are inappropriate for medical and/or religious reasons. While federal laws provide certain immunity from liability due to harm that vaccination causes a person, those liability protections are limited to particular entities such as vaccine manufacturers and medical professionals having administered the vaccination(s). Those liability protections do not extend to organizations such as yours which choose to require vaccination of their guests/customers.

Fifth, your policy imposes **burdens of additional time, expense, and requirements** to obtain COVID "vaccinations" or "COVID tests" on your customers (including Mr. Bush) after those customers had already purchased tickets to shows at your theatres. To impose such new requirements, expenses, and burdens after customers had already made those purchases when no law requires you to do so is both unfair and deceptive business practice on your part.

Sixth, your policy claimed that the vaccination and test requirements you are imposing on customers are to "stop the spread" of COVID-19. Yet COVID-19 has a lower infection fatality rate than infections of other germs transmitted between people that are still in existence, including Ebola, Marburg virus, pneumonic plague, hantavirus pulmonary syndrome, diphtheria, meningitis, respiratory syncytial virus, measles, meningitis, and tuberculosis. Your policy thus unfairly discriminates against people infected with one specific germ while making no equivalent effort to curtail the spread of other, more dangerous infectious diseases.

Seventh, we submit that Masks are not effective for prevention of the spread of COVID-19 [iv], have known harms [v], and are not approved to prevent the spread of SARS-CoV-2 infections. An EUA from the FDA, mentioned above, is for products of an investigational or experimental nature. Your policy is deceptive and unfair by failing to disclose that your mask requirement is experimental and that wearing masks is known to be harmful.

Moreover, by unilaterally requiring persons to wear masks without having specified that those masks be tested, effective, or approved for the function of preventing the spread of infections, you have made a deceptive claim. The U.S. Food and Drug Administration's (FDA) Emergency Use Authorization (EUA) for surgical and/or cloth masks requires that, "The product is not labeled in such a manner that would misrepresent the product's intended use; for example, the labeling must not state or imply that the product is intended for antimicrobial or antiviral protection or related uses or is for use such as infection prevention or reduction."

The statute granting the FDA the power to authorize a medical product for emergency use requires that the person being administered the product be advised of his or her right to refuse administration of the product. This statute further recognizes the well-settled doctrine that medical experiments, or "clinical research," may not be performed on human subjects without the express, informed consent of the individual receiving treatment. As C.F.R. § 50.20 states, "An investigator shall seek such consent only under circumstances that provide the prospective

subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative."

Wearing face coverings/masks is medically contraindicated for certain persons. Therefore, your policy requiring people to wear masks without regard for their medical needs violates the federal Americans with Disabilities Act. Title II of the Americans with Disabilities Act (ADA) provides that no individual with a disability shall, by reason of such disability, be excluded from participation in or be denied the benefits of the services, program, or activities of a public entity, or be subjected to discrimination by any such entity. Title III of the ADA prohibits discrimination on the basis of disability in public accommodations, such as your theatres. As requiring of customers evidence of such medical needs or disability would violate the spirit and intent of the law, you may not require such evidence or information from guests/customers.

Some religions, creeds, physical disabilities, and/or mental disabilities prohibit or contraindicate the wearing of masks or face coverings. Therefore, your policy violates M.G.L. Chapter 272 Section 92A. The statute prohibits public accommodations (including "an auditorium, theatre, music hall, meeting place or hall, including the common halls of buildings") from depriving people of any, "religious sect, creed… deafness or blindness, or any physical or mental disability" of the "full enjoyment of the accommodations, advantages, facilities or privileges offered to the general public." Further, the statute states that, "Any person who shall violate any provision of this section, or who shall aid in or incite, cause or bring about, in whole or in part, such a violation shall be punished by a fine of not more than one hundred dollars, or by imprisonment for not more than thirty days, or both."

Massachusetts General Laws Chapter 93A, Section 2(a) declares unlawful unfair or deceptive acts or practices in the conduct of any trade or commerce. In the case of *Nei vs. Burley*, 388 Mass. 307 (1983), the Supreme Judicial Court held that the terms "unfair or deceptive" are sufficiently open-ended to embrace causes of action for which there are no common law analogies.

Notwithstanding the above, your policy cites "City of Boston guidelines", however, your policy is in violation of the Boston Public Health Commission's Order Requiring Face Coverings In The City Of Boston dated August 20, 2021. [vi] That Order states that, "face coverings are not required for children under two years of age, anyone who has trouble breathing, anyone who is unconscious, incapacitated or otherwise unable to remove the mask without assistance, or anyone who due to disability is unable to wear a mask." Furthermore, orders, mandates, guidance, advisories, and the like are not laws and regardless of their issuance you are obligated to comply with applicable laws. Accordingly, you are hereby notified that face coverings are medically inappropriate for Michael Bush and that face coverings, COVID vaccination, and COVID tests violate his religious convictions. He and his companion(s) shall attend the shows for which he has or may purchase tickets without meeting the requirements of your unlawful policy and he/they is/are to be afforded full enjoyment of the accommodations, advantages, facilities or privileges offered to the general public without coercion or discrimination.

Your failure to respond to this 93A Demand Letter within thirty (30) days offering a reasonable settlement will compel the commencement of a lawsuit under said Chapter 93A. We construe a reasonable offer of settlement to be that within the next thirty (30) days you:

1. Inform your customers via email that you have rescinded the above-identified unfair, deceptive, and unlawful policy;

2. Respond to this letter with evidence that you have rescinded the above policy and written assurance that you shall henceforth refrain from improper medical claims, experimentation without consent, and religious and medical discrimination; and

3. Pay Bush Five Thousand Dollars ("$5,000.00") for your unfair and deceptive conduct and violations of his legal rights, as well as One Thousand Dollars ("$1,000.00") in Attorney's Fees, including interest thereupon.

If a suit is commenced against the Boch Center and its conduct is found to be unfair and/or deceptive, Bush will be awarded his damages and may also automatically receive an award whereby the Boch Center may be required to pay his attorney's fees thus far as well as those required for protracted litigation. Furthermore, if a Court determines that your conduct was willfully or knowingly **unfair or deceptive**, the Court may award Bush up to three times, but not less than two times, his actual damage.

This letter is being sent to you by Certified Mail, Return Receipt Requested, as well as U.S. First Class Mail, Postage Pre-Paid.

Yours truly,

Richard C. Chambers, Jr., Esq.

Enclosure

cc: Client

---

[i] https://www.wsj.com/articles/zero-covid-coronavirus-pandemic-lockdowns-china-australia-new-zealand-11628101945

[ii] https://www.cnbc.com/2021/07/30/cdc-study-shows-74percent-of-people-infected-in-massachusetts-covid-outbreak-were-fully-vaccinated.html and https://www.medrxiv.org/content/10.1101/2021.07.31.21261387v4

[iii] https://www.theblaze.com/op-ed/horowitz-15-studies-that-indicate-natural-immunity-from-prior-infection-is-more-robust-than-the-covid-vaccines and https://www.medrxiv.org/content/10.1101/2021.08.24.21262415v1

[iv] https://www.acpjournals.org/doi/10.7326/M20-6817

[v] https://www.mdpi.com/1660-4601/18/8/4344/htm

[vi] https://www.boston.gov/sites/default/files/file/2021/08/BPHC%20COVID-19%20Face%20Coverings%20Order%208%2020%202021.pdf

Exhibit 10

DLA Piper LLP (US)
33 Arch Street
26th Floor
Boston, Massachusetts 02110-1447
www.dlapiper.com

Bruce E. Falby
T 617.406.6020
F 617.406.6120

September 27, 2021

BY FIRST-CLASS MAIL

Richard C. Chambers, Jr., Esq.
Chambers Law Office
220 Broadway, Suite 404
Lynnfield, MA 01940

Re: Mr. Michael Bush
280 Lowell Street
Carlisle, MA 01741

Dear Mr. Chambers:

I represent The Wang Center for the Performing Arts, Inc. d/b/a Boch Center ("Boch Center"). This letter responds to your letter dated September 16, 2021.

Your assertions of unfair and/or deceptive trade practices have no merit or good faith basis. Among other reasons, (i) the COVID vaccination, testing, and mask requirements of which you complain have been reasonably and responsibly adopted by virtually every indoor performing arts and sports venue in Boston (including TD Garden) in response to the resurgence of the COVID-19 pandemic; (ii) many performers are insisting on these requirements so without them performances would simply be cancelled; and (iii) a full ticket price refund has been provided upon request to any patron not wishing to comply with the requirements. Further, and responding in order to your paragraphs purporting to specify unfair and deceptive trade practices:

First, your letter does not state whether your client has a naturally acquired immunity and therefore any standing to raise this issue. In any event, anyone with a naturally acquired immunity can gain admittance by showing proof of a negative test or by rapid testing negative in the Wang Theatre lobby, where rapid tests administered by Cataldo Ambulance Service (a primary state partner in providing COVID testing) are available for $30.00/test with a discounted rate of $10.00 for someone who cannot be vaccinated for religious, medical or age reasons.

Second, there is nothing unfair or deceptive about requiring proof of vaccination, the effectiveness of which is a matter of public knowledge.

Third, there is nothing unfair or deceptive about alternatively requiring a negative COVID test, the accuracy of which is a matter of public knowledge.

Fourth, your letter does not state whether a vaccine is inappropriate for your client for medical or religious reasons and thus whether your client has standing to raise this issue. In any event, anyone for whom a vaccine is not appropriate for medical or religious reasons can gain admittance by showing proof of a negative test or by rapid testing negative in the Wang Theatre lobby.

DLA PIPER

Fifth, your client had the option of avoiding any burden of time or expense simply by requesting a refund of the ticket price. My client has issued a full refund to anyone requesting one and will also issue a full refund to anyone who rapid tests positive on-site.

Sixth, my client's statement that "The Boch Center is committed to helping stop the spread of COVID-19" is accurate and neither unfair nor deceptive. The goal of stopping the spread of COVID-19 is laudatory and in the public interest, not actionable.

Seventh, masks are required indoors by the City of Boston and adhering to the City's indoor mask mandate is neither unfair nor deceptive.

In a reasonable offer of settlement, my client is willing to refund the full purchase price of tickets purchased by your client.

If you do pursue litigation, my client will seek Rule 11 sanctions as appropriate.

Very truly yours,

/s/ Bruce E. Falby

Bruce E. Falby

BEF/clc

Exhibit 11

Chambers Law Office

Richard C. Chambers, Jr.
Joseph Spinale †
John P. Rauseo †
Janis Stanziani †
Matthew Littleton *
Kevin McGrath *
Robert Joost *

Paralegal *
Of Counsel †

Telephone: (781) 581-2031
Facsimile: (781) 581-8449

220 Broadway, Suite 404
Lynnfield, Massachusetts 01940

www.ChambersLawOffice.com

November 15, 2021

SENT VIA CERTIFIED MAIL 7016 0750 0000 1779 0305,
RETURN RECEIPT REQUESTED AND U.S. FIRST CLASS MAIL

Bruce E. Falby, Esq.
DLA Piper, LLP
33 Arch Street, 26th Floor
Boston, MA 02110

RE: Mr. Michael Bush
280 Lowell Street
Carlisle, MA 01741

Dear Attorney Falby:

Thank you for your letter dated September 27, 2021, in response to my client Michael Bush's ("Bush") M.G.L. Ch. 93A Notice and Demand Letter. Though your letter attempted to clarify The Wang Center For The Performing Arts, Inc., d/b/a. Boch Center's ("Boch Center") positions on this matter, it failed to address or resolve some of the fundamental medical and legal discrepancies of the Boch Center's policy in question. It also gave the distinct impression that you had not read and/or chose to ignore the legal and medical references I cited in Bush's Demand letter.

Your letter claimed that other indoor performing arts and sports venues in Boston have implemented similar COVID-19 vaccination, testing, and mask requirements policies as if that excuses or justifies The Boch Center violating the Massachusetts and federal laws I cited in Bush's 93A Demand letter. It does not. Moreover, Bush's dispute is with Boch Center, not other Boston venues.

Your letter also claimed that many performers are insisting on these requirements. Obviously, if the COVID-19 "vaccines" work as you imply, there is no reason for performers or The Boch Center's personnel to insist on anyone but themselves taking them. Furthermore, the performers' preferences do not nullify Boch Center's obligations to honor the terms upon which Bush bought tickets to the shows, which involved no requirements for customers to wear face masks or take vaccinations and/or tests.

You stated that, "there is nothing unfair or deceptive about requiring proof of vaccination, the effectiveness of which is a matter of public knowledge." We agree that the COVID-19 "vaccines'" effectiveness (or lack thereof) *is* a matter of public knowledge. As I noted in Bush's Demand letter, it had been public knowledge and well-documented in the medical literature well before the Boch Center issued its policy that the COVID-19 "vaccines" do not stop infection or transmission of the SARS-CoV-2 virus. Thus, there is no justification for Boch Center to demand proof of such vaccination. It was not clear whether you were meaning to imply that the "vaccines" are effective or ineffective, as you did not provide any substantiation for your vague claim.

You also stated that, "there is nothing unfair or deceptive about alternatively requiring a negative COVID test, the accuracy of which is a matter of public knowledge." If you mean to refer to the unapproved COVID tests with EUAs from the FDA (the only kind legally available), then you are correct again. That they are notoriously unreliable *has* been public knowledge and they may not be required of anyone without informed consent to participate in such medical experimentation, as I explained in Bush's Demand letter. As I noted in the Demand letter, Bush has religious objections to such tests, which your response letter ignored.

Your letter also failed to address that the FDA has not approved face masks to stop the spread of viral respiratory infections and that wearing face masks has known harms. I provided a medical reference of such harms in the Demand letter. Your letter simply ignored both those face mask discrepancies of Boch Center's policy.

Your letter mentioned that "masks" are required indoors by the City of Boston. Yet you failed to address, much less refute, that The Boch Center's policy is in violation of the Boston Public Health Commission's pertinent order, which was quoted and linked to in Bush's Demand letter. Your letter also failed to address the fact that you were informed in Bush's Demand letter that face masks are medically inappropriate for Bush. By failing to acknowledge and honor that fact, you have provided a response in bad faith and further demonstrated Boch Center's intent to willfully violate the applicable state and federal civil rights laws cited.

You also claimed that The Boch Center stating its policy is intended to help stop the spread of COVID-19 is accurate despite my having shown in Bush's Demand letter that stopping the spread of COVID-19 is impossible. Therefore, the claim is obviously unfair and deceptive. Yet you provided no substantiation for your statement that the claim is accurate.

After having failed to address the Boch Center's policy's violations of state and federal civil rights laws of which Bush informed Boch Center, your letter proceeded to merely offer Bush a refund for the purchase price of his tickets. That is precisely the sort of unfair conduct and inhumane discrimination and segregation that the Massachusetts Consumer Protection Law (M.G.L. Ch. 93A) and the civil rights laws cited are intended to prohibit and punish. Thus, your letter perpetuated the unfair conduct of Boch Center towards Bush and provided further evidence of Boch Center's disdain for civil and constitutional rights. Your letter is admissible as evidence in court.

You ended your letter with a threat to seek "sanctions" per an unspecified "Rule 11". Given that: 1) Bush's Demand letter was not a legal pleading, 2) Bush's Demand letter substantiated its claims with an exhibit and multiple medical and legal citations, and 3) your response letter provided no substantiation or medical or legal references for your claims, it is not Bush who needs concern himself with potential "sanctions" for meritless claims.

In the interest of bringing Boch Center's legal violations to a swift end and enabling Bush to attend the upcoming shows without incurring further damages or expenses, Bush again gives Boch Center the opportunity to:

1. Inform their customers via email that they have rescinded their unfair, deceptive, and unlawful policy;
2. Respond to this letter with evidence that they have rescinded the above policy and written assurance that they shall henceforth refrain from improper medical claims, experimentation without consent, and religious and medical discrimination; and
3. Pay Bush Five Thousand Dollars ("$5,000.00") for their unfair and deceptive conduct, violations of his legal rights, as well as One Thousand Dollars ("$1,000.00") in Attorney's Fees, including interest thereupon.

To be clear, it is not that Boch Center cannot have *any* policy regarding COVID-19 vaccination, testing, or face masks. It is that Boch Center's current policy is in violation of applicable laws (prohibiting unfair and deceptive claims, uninformed and harmful medical experimentation, and medical and religious discrimination, etc.), as explained in Bush's Demand letter. If Boch Center wishes to maintain a policy of some kind, it must be made lawful and Bush's above reasonable demands must be met. Bush is open to collaboration and assisting with the creation of a lawful, honest, and ethical policy.

Should Boch Center fail to meet Bush's above reasonable demands within seven (7) days of receipt of this letter, Bush intends to sue.

Bear in mind that the next show for which Bush has tickets is scheduled for December 11, 2021. Regardless of litigation or other efforts, if that date arrives without The Boch Center having resolved this matter in accordance with applicable laws and in fairness to Bush, The Boch Center will have exacerbated Bush's damages.

Yours truly,

Richard C. Chambers, Jr., Esq.

cc: Client

Exhibit 1a

Subject: Important Safety Information For Cirque Dreams Holidaze

From: Boch Center - To: bmoc54@verizon.net - Cc: - Date: December 2, 2021 at 4:58 PM

Dear Patron,
We are so excited to welcome you to our theatres!

Before you come to our theatres or purchase tickets, make sure you please read the health, vaccine and entry policy below. Vaccinations or proof of negative Covid-19 test are required **FOR ALL PATRONS** at our theatres **REGARDLESS OF AGE.** Masks are also required to be worn in our theatres per City of Boston requirements.

MASKS REQUIRED
Everyone in our theatres must wear appropriate face coverings at all times, including during the show, except while eating or drinking. All face coverings must cover the nose and mouth and comply with the CDC guidelines for acceptable face coverings.

VACCINATIONS OR NEGATIVE COVID-19 TEST REQUIRED FOR AGES 12 AND UNDER
Everyone under the age of 12 must be fully vaccinated with an FDA or WHO authorized vaccine OR provide a negative Covid test, taken within 72 hours, to attend a show. At home tests will not be accepted. Be ready to show proof of vaccination and your negative Covid test results at the theatre. To confirm your entrance eligibility the following proof will be accepted:

- Two doses of an FDA or WHO authorized Covid-19 vaccine, received at least 14 days before the performance
- A negative Covid-19 PCR test taken within 72 hours of the performance
- A negative Covid-19 rapid antigen test taken within 72 hours of the performance

You may present proof of vaccination or a negative test on paper or a smartphone. At-home rapid tests will not be accepted.

APPROVED VACCINES: Pfizer/BioNTech (2 dose), Moderna (2 dose), Janssen/Johnson & Johnson, Oxford/AstraZeneca, Serum Institute of India-Covishield, Sinopharm (Beijing), Sinovac

VACCINATIONS OR NEGATIVE COVID-19 TEST REQUIRED FOR AGES 12+
Everyone ages 12 and older must be fully vaccinated with an FDA or WHO authorized vaccine OR provide a negative Covid test, taken within 72 hours, to attend a show At

home tests will not be accepted. Be ready to show proof of vaccination and your negative Covid test results at the theatre. To confirm your entrance eligibility the following proof will be accepted:

- Two doses of an FDA or WHO authorized two dose Covid-19 vaccine, received at least 14 days before the performance
- A negative Covid-19 PCR test taken within 72 hours of the performance
- A negative Covid-19 rapid antigen test taken within 72 hours of the performance

You may present proof of vaccination or a negative test on paper or a smartphone. At-home rapid tests will not be accepted.

APPROVED VACCINES: Pfizer/BioNTech (2 dose), Moderna (2 dose), Janssen/Johnson & Johnson, Oxford/AstraZeneca, Serum Institute of India-Covishield, Sinopharm (Beijing), Sinovac

ON-SITE COVID-19 TESTING

As an added service, The Boch Center is providing on-site rapid Covid-19 testing on a first-come first-served basis. On-site testing is available beginning 3 hours prior to curtain time on the day of your performance. **To avoid long wait times we highly recommend getting tested before coming to our theatres. On-site testing should be used as a last resort for those who have either forgotten their vaccination card or are unable to receive a test ahead of time. Please plan to arrive early if you are utilizing our on-site testing. Each test takes 15-20 minutes once you reach the front of the line.**

- There is a $30 charge per test for anyone age 12 and above
- There is a $10 charge for children under the age of 12
- There will be free testing for children under the age of 12 for the following Holiday performances:
  - A Christmas Story, The Musical – December 7 – 19
  - Cirque Dreams Holidaze – December 10 -12
  - Urban Nutcracker – December 18 - 22

PHOTO ID REQUIRED

Along with proof of vaccination, all guests 18 years or older must also present a government-issued photo ID, such as a driver's license or passport.
Guests under 18 do not need to show ID if they are accompanied by an adult with a valid form of ID
Children under 12 must be accompanied by an adult who meets the above requirements.

By purchasing tickets to an event, you agree to abide by these, and any other, health and safety measures that may be in effect at the time of the event. Please note that restrictions and safety protocols may vary by performance. Be sure to visit your specific show's event details page and to carefully read our pre-performance emails for important information pertaining to your performance.

Thank you for reading and following all the theatres' policies. We hope you enjoy the show!

MORE INFO

The Boch Center is a 501(c)(3) nonprofit institution.

We are an innovator and guardian of iconic venues, providing relevant and inclusive performing arts entertainment and cultural educational experiences for the most diverse audiences possible.

Find A Show | Donate Today | Learn About Our Outreach Programs

PROUD SPONSORS

Boch Center | 270 Tremont Street, Boston, MA 02116

Exhibit 13

THE WALL STREET JOURNAL.

AUGUST 04, 2021

Eradication of Covid Is a Dangerous and Expensive Fantasy; It seemed to work in New Zealand and Australia, but now ruinous, oppressive lockdowns are back.

By Jay Bhattacharya and Donald J. Boudreaux

Much of the pathology underlying Covid policy arises from the fantasy that it is possible to eradicate the virus. Capitalizing on pandemic panic, governments and compliant media have used the lure of zero-Covid to induce obedience to harsh and arbitrary lockdown policies and associated violations of civil liberties.

Among all countries, New Zealand, Australia and especially China have most zealously embraced zero-Covid. China's initial lockdown in Wuhan was the most tyrannical. It infamously locked people into their homes, forced patients to take untested medications, and imposed 40-day quarantines at gunpoint.

On March 24, 2020, New Zealand imposed one of the most onerous lockdowns in the free world, with sharp restrictions on international travel, business closures, a prohibition on going outside, and official encouragement of citizens to snitch on neighbors. In May 2020, having hit zero-Covid, New Zealand lifted lockdown restrictions, except quarantines for international travelers and warrantless house searches to enforce lockdown.

Australia also took the zero-Covid route. While the initial steps focused on banning international travel, the lockdowns there also involved closed schools, occasional separation of mothers from premature newborns, brutal suppression of protests, and arrests for wandering more than 3 miles from home.

New Zealand's and Australia's temporary achievement of zero-Covid and China's claimed success were greeted with fanfare by the media and scientific journals. China's authoritarian response seemed so successful—despite the country's record of lying about the virus—that panicked democratic governments around the world copied it. The three countries lifted their lockdowns and celebrated.

Then, when Covid came back, so did the lockdowns. Each government has had multiple opportunities to glory in achieving zero-Covid by hairshirt. Australia's current lockdowns in Sydney are now enforced by military patrols alongside strict warnings from health officials against speaking with neighbors. After Prime Minister Boris Johnson announced that the U.K. must "learn to live with" the virus, New Zealand's minister for Covid-19 response, Chris Hipkins, imperiously responded, "That's not something that we have been willing to accept in New Zealand."

Humanity's unimpressive track record of deliberately eradicating contagious diseases warns us that lockdown measures, however draconian, can't work. Thus far, the number of such diseases so eliminated stands at two—and one of these, rinderpest, affected only even-toed ungulates. The lone human infectious disease we've deliberately eradicated is smallpox. The bacterium responsible for the Black Death, the 14th-century outbreak of bubonic plague, is still with us, causing infections even in the U.S.

While the eradication of smallpox—a virus 100 times as deadly as Covid—was an impressive feat, it shouldn't be used as a precedent for Covid. For one thing, unlike smallpox, which was carried only by humans, SARS-CoV-2 is also carried by animals, which some hypothesize can spread the disease to humans. We will need to rid ourselves of dogs, cats, mink, bats and more to get to zero.

For another, the smallpox vaccine is incredibly effective at preventing infection and severe disease, even after exposure to disease, with protection lasting five to 10 years. The Covid vaccines are far less effective at preventing spread.

And smallpox eradication required a concerted global effort lasting decades and unprecedented cooperation among nations. Nothing like this is possible today, especially if it requires a perpetual lockdown in every country on earth. That's simply too much to ask, especially of poor countries, where lockdowns have proved devastatingly harmful to public health. If even one nonhuman reservoir or a single country or region that fails to adopt the program, zero-Covid would fail.

The costs of any eradication program are immense and must be justified before the government pursues such a goal. These costs include a sacrifice of non-health-related goods and services and other health priorities—forgone prevention and treatment of other diseases. The consistent failure of government officials to recognize the harms of lockdowns—often citing the precautionary principle—disqualifies Covid as a candidate for eradication.

The only practical course is to live with the virus in the same way that we have learned to live over millennia with countless other pathogens. A focused protection policy can help us cope with the risk. There is a thousand-fold difference in the mortality and hospitalization risk posed by virus to the old relative to the young. We now have good vaccines that have helped protect vulnerable people from the ravages of Covid wherever they have been deployed. Offering the vaccine to the vulnerable everywhere, not the failed lockdowns, should be the priority to save lives.

We live with countless hazards, each of which we could but sensibly choose not to eradicate. Automobile fatalities could be eradicated by outlawing motor vehicles. Drowning could be eradicated by outlawing swimming and bathing. Electrocution could be eradicated by outlawing electricity. We live with these risks not because we're indifferent to suffering but because we understand that the costs of zero-drowning or zero-electrocution →

Exhibit 19

Subject: Important Vaccine & Entry Policy Update

From: Boch Center - To: bmoc54@verizon.net - Cc: - Date: January 5, 2022 at 4:42 PM

Our Covid-19 Policy and Safety Measures **will be changing on January 15, 2022** per the City of Boston's new vaccine requirement for indoor spaces.

To enter our theatres the following criteria must be met:

- For patrons ages 12 and up, full vaccination is required to attend any performance.
- For patrons ages 5-11, full vaccination is required **beginning March 1, 2022.** Prior to March 1, patrons ages 5-11 can provide a negative Covid-19 PCR test or a negative Covid-19 rapid antigen test taken within 72 hours of the performance.
- For patrons ages 2-4, a negative Covid-19 PCR test or a negative Covid-19 rapid antigen test taken within 72 hours of the performance is required. At home tests will not be accepted.
- Masks are also required to be worn in our theatres.

MASKS REQUIRED

Everyone in our theatres must wear appropriate face coverings at all times, including during the show, except while eating or drinking. All face coverings must cover the nose and mouth and comply with the CDC guidelines for acceptable face coverings.

VACCINATIONS REQUIRED FOR AGES 12+

Everyone ages 12 and older must be fully vaccinated with an FDA or WHO authorized vaccine, to attend a show. Be ready to show proof of vaccination and a valid Government issued ID before entering the theatre. To confirm your entrance eligibility the following proof will be accepted:

- Two doses of an FDA or WHO authorized Covid-19 vaccine, received at least 14 days before the performance

You may present proof of vaccination on paper or a smartphone.

VACCINATIONS REQUIRED FOR AGES 5-11 BEGINNING MARCH 1, 2022
Everyone ages 5-11 must be fully vaccinated with an FDA or WHO authorized vaccine, to attend a show. Be ready to show proof of vaccination before entering the theatre. To confirm your entrance eligibility the following proof will be accepted:

- Two doses of an FDA or WHO authorized Covid-19 vaccine, received at least 14 days before the performance

You may present proof of vaccination on paper or a smartphone.

NEGATIVE COVID-19 TEST REQUIRED FOR AGES 2-4
Everyone ages 2-4 must provide a negative Covid-19 test, taken within 72 hours, to attend a show. At home tests will not be accepted. Be ready to show your negative Covid-19 test results at the theatre. To confirm your entrance eligibility the following proof will be accepted:

- A negative Covid-19 PCR test taken within 72 hours of the performance
- A negative Covid-19 rapid antigen test taken within 72 hours of the performance

Please note that restrictions and safety protocols may vary by performance. Be sure to visit your specific show's event details page and to carefully read our pre-performance emails for important information pertaining to your performance.

MORE INFO & SAFETY UPGRADES

The Boch Center is a 501(c)(3) nonprofit institution.

We are an innovator and guardian of iconic venues, providing relevant and inclusive performing arts entertainment and cultural educational experiences for the most diverse audiences possible.

Find A Show | Donate Today | Learn About Our Outreach Programs

PROUD SPONSORS

Boch Center | 270 Tremont Street, Boston, MA 02116

CIVIL ACTION COVER SHEET

DOCKET NUMBER: 22.628

Trial Court of Massachusetts
The Superior Court

COUNTY: Middlesex Superior Court (Woburn)

Plaintiff	Michael Bush	Defendant:	The Wang Center for the Performing Arts, Inc. d/b/a Boch Center
ADDRESS:	280 Lowell Street	ADDRESS:	
Carlisle, MA 01741		270 Tremont Street	
		Boston, MA 02116	
Plaintiff Attorney:	Richard C. Chambers, Jr., Esq.	**Defendant Attorney:**	
ADDRESS:	Chambers Law Office	ADDRESS:	
220 Broadway, Suite 404			
Lynnfield, MA 01940			
BBO:	651251	BBO:	

TYPE OF ACTION AND TRACK DESIGNATION (see instructions section below)

CODE NO.	TYPE OF ACTION (specify)	TRACK	HAS A JURY CLAIM BEEN MADE?
A01	Services, Labor and Materials	F	☒ YES ☐ NO

*If "Other" please describe:

Is there a claim under G.L. c. 93A? ☒ YES ☐ NO

Is there a class action under Mass. R. Civ. P. 23? ☐ YES ☒ NO

STATEMENT OF DAMAGES PURSUANT TO G.L. c. 212, § 3A

The following is a full, itemized and detailed statement of the facts on which the undersigned plaintiff or plaintiff's counsel relies to determine money damages. For this form, disregard double or treble damage claims; indicate single damages only.

FILED
IN THE OFFICE OF THE
CLERK OF COURTS
FOR THE COUNTY OF MIDDLESEX
JAN 31 2022
CLERK

TORT CLAIMS

A. Documented medical expenses to date
1. Total hospital expenses
2. Total doctor expenses
3. Total chiropractic expenses
4. Total physical therapy expenses
5. Total other expenses (describe below)

Subtotal (1-5): **$0.00**

B. Documented lost wages and compensation to date
C. Documented property damages to date
D. Reasonably anticipated future medical and hospital expenses
E. Reasonably anticipated lost wages
F. Other documented items of damages (describe below)

TOTAL (A-F): **$0.00**

G. Briefly describe plaintiff's injury, including the nature and extent of injury:

CONTRACT CLAIMS

☐ This action includes a claim involving collection of a debt incurred pursuant to a revolving credit agreement. Mass. R. Civ. P. 8.1(a).

Item #	Detailed Description of Each Claim	Amount
1.	Unfair and deceptive conduct in violation of the Plaintiff's consumer and civil rights	$800,000.00
	Total	**$800,000.00**

Signature of Attorney/Unrepresented Plaintiff: X Richard C. Chambers Date: January 28, 2022

RELATED ACTIONS: Please provide the case number, case name, and county of any related actions pending in the Superior Court.

CERTIFICATION PURSUANT TO SJC RULE 1:18

I hereby certify that I have complied with requirements of Rule 5 of the Supreme Judicial Court Uniform Rules on Dispute Resolution (SJC Rule 1:18) requiring that I provide my clients with information about court-connected dispute resolution services and discuss with them the advantages and disadvantages of the various methods of dispute resolution.

Signature of Attorney/Unrepresented Plaintiff: X Richard C. Chambers Date: January 28, 2022

L1

COMMONWEALTH OF MASSACHUSETTS

MIDDLESEX, ss.

SUPERIOR COURT DEPARTMENT
CIVIL ACTION NO.: 2281CV00628

RECEIVED
2/24/2022

MICHAEL BUSH,
Plaintiff,
v.
THE WANG CENTER FOR THE PERFORMING ARTS, doing business as BOCH CENTER.
Defendants.

ASSENTED TO NOTICE OF WITHDRAWAL

Please enter my Notice of Withdrawal on behalf of the Plaintiff, MICHAEL BUSH, in the above-captioned matter. Undersigned counsel has spoken with the Plaintiff, and he will be moving forward in a *pro se* capacity.

I, Plaintiff Michael Bush, hereby assent to the Withdrawal of Attorney Richard C. Chambers, Jr., as attorney of record in the above matter and I will be moving forward in a *pro se* capacity in this matter.

Michael Bush

Plaintiff, Michael Bush

DATED: February 24, 2022

RM

Richard C. Chambers, Jr., Esq.
BBO#: 651251
Chambers Law Office
220 Broadway, Suite 404
Lynnfield, MA 01940
Office: (781) 581-2031
Cell: (781) 363-1773
Fax: (781) 581-8449
Email: Richard@chamberslawoffice.com

DATED: February 24, 2022

Richard C. Chambers, Jr., Esq.

ϕ 9A

L1

COMMONWEALTH OF MASSACHUSETTS

MIDDLESEX, ss.

SUPERIOR COURT DEPARTMENT
CIVIL ACTION NO.: 2281CV00628

RECEIVED
2/24/2022

MICHAEL BUSH,
Plaintiff,
v.
THE WANG CENTER FOR THE PERFORMING ARTS, doing business as BOCH CENTER.
Defendants.

ASSENTED TO NOTICE OF WITHDRAWAL

Please enter my Notice of Withdrawal on behalf of the Plaintiff, MICHAEL BUSH, in the above-captioned matter. Undersigned counsel has spoken with the Plaintiff, and he will be moving forward in a *pro se* capacity.

I, Plaintiff Michael Bush, hereby assent to the Withdrawal of Attorney Richard C. Chambers, Jr., as attorney of record in the above matter and I will be moving forward in a *pro se* capacity in this matter.

Michael Bush
Plaintiff, Michael Bush

DATED: February 24, 2022

DENIED WITHOUT PREJUDICE, MUST COMPLY WITH RULE 9A. DMT 3/1/22

RM

Chambers Law Office

Richard C. Chambers, Jr.
Joseph Spinale
John P. Rauseo †
Janis Stanziani †
Matthew Littleton *
Robert Joost *
Kevin McGrath *

Paralegal *
Of Counsel †

Telephone: (781) 581-2031
Facsimile: (781) 581-8449

220 Broadway, Suite 404
Lynnfield, Massachusetts 01940

www.ChambersLawOffice.com

March 15, 2022

SENT VIA U.S. FIRST CLASS MAIL

The Wang Center for the Performing Arts
D/B/A Boch Center
270 Tremont Street
Boston, MA 02116

Re: *Michael Bush v. The Wang Center for the Performing Arts, doing business as Boch Center*
C.A. No.: 2281CV00628

Dear Sir/Madam,

Pursuant to Superior Court Rule 9A, please enclosed find copies of the following document:

- Assented to Motion to Withdraw.

Kindly provide my office with any opposition within the time period allowed by Superior Court Rule 9A.

Thank you for your assistance in this matter. Should you have any questions or concerns, please do not hesitate to contact my office.

Yours truly,

Richard C. Chambers, Jr., Esq.

Enclosure

cc: Michael Bush

COMMONWEALTH OF MASSACHUSETTS

MIDDLESEX, ss.

SUPERIOR COURT DEPARTMENT
CIVIL ACTION NO.: 2281CV00628

MICHAEL BUSH,

Plaintiff,

v.

THE WANG CENTER FOR THE PERFORMING ARTS, doing business as BOCH CENTER.

Defendants.

ASSENTED TO MOTION TO WITHDRAW

I, Richard C. Chambers, Jr., Esq., ("Counsel") for the Plaintiff, MICHAEL BUSH, ("Plaintiff") in the above-entitled action, respectfully request that this Honorable Court allow me to withdraw my appearance on behalf of the Plaintiff.

As grounds and reasons therefore, Counsel submits that he has spoken with the Plaintiff, who advised Counsel that he would moving forward in a *pro se* capacity.

I, Michael Bush, hereby assent to the Withdrawal of Attorney Richard C. Chambers, Jr., as attorney of record in the above-entitled action and I will be moving forward in a *pro se* capacity in this matter.

Michael Bush

Plaintiff, Michael Bush

DATED: March 15, 2022

Respectfully submitted,

DATED: March 15, 2022

Richard C. Chambers, Jr., Esq.
BBO#: 651251
Chambers Law Office
220 Broadway, Suite 404
Lynnfield, MA 01940
Office: (781) 581-2031
Cell: (781) 363-1773
Fax: (781) 581-8449
Email: Richard@chamberslawoffice.com

CERTIFICATE OF SERVICE

I, Richard C. Chambers, Jr., Esq., hereby certify that I caused a true copy of the foregoing document to be served upon the Defendant, via U.S. First Class Mail, postage pre-paid, as follows:

The Wang Center for the Performing Arts
D/B/A Boch Center
270 Tremont Street
Boston, MA 02116

DATED: March 15, 2022

Richard C. Chambers, Jr., Esq.

Commonwealth of Massachusetts

MIDDLESEX,SS.

TRIAL COURT OF THE COMMONWEALTH
SUPERIOR COURT DEPARTMENT
CIVIL DOCKET NO. 2281CV00628

Michael Bush, PLAINTIFF(S),

V.

The Wang Center for the Performing Arts, Inc. doing business as Boch Center, DEFENDANT(S)

SUMMONS

THIS SUMMONS IS DIRECTED TO The Wang Center for the Performing Arts, Inc. doing business as Boch Center (Defendant's name)

You are being sued. The Plaintiff(s) named above has started a lawsuit against you. A copy of the Plaintiff's Complaint filed against you is attached to this summons and the original complaint has been filed in the Middlesex Superior Court. **YOU MUST ACT PROMPTLY TO PROTECT YOUR RIGHTS.**

1. **You must respond to this lawsuit in writing within 20 days.** If you do not respond, the court may decide the case against you and award the Plaintiff everything asked for in the complaint. You will also lose the opportunity to tell your side of the story. You must respond to this lawsuit in writing even if you expect to resolve this matter with the Plaintiff. **If you need more time to respond, you may request an extension of time in writing from the Court.**
2. **How to Respond.** To respond to this lawsuit, you must file a written response with the court **and** mail a copy to the Plaintiff's Attorney (or the Plaintiff, if unrepresented). You can do this by:
   a. Filing your **signed original** response with the Clerk's Office for Civil Business, Middlesex Superior Court, 200 Tradecenter Dr. Woburn MA 01801 (address), by mail or in person, **AND**
   b. Delivering or mailing a **copy** of your response to the ~~Plaintiff's Attorney~~/Plaintiff at the following address: ~~220 Broadway Suite 104 Lynnfield MA 01940~~ 280 Lowell Street, Carlisle MA 01741
3. **What to include in your response.** An **"Answer"** is one type of response to a Complaint. Your Answer must state whether you agree or disagree with the fact(s) alleged in each paragraph of the Complaint. Some defenses, called affirmative defenses, must be stated in your Answer or you may lose your right to use them in court. If you have any claims against the Plaintiff (referred to as **counterclaims**) that are based on the same facts or transaction described in the Complaint, then you must include those claims in your Answer. Otherwise, you may lose your right to sue the Plaintiff about anything related to this lawsuit. If you want to have your case heard by a jury, you must **specifically** request a jury trial in your Answer or in a written demand for a jury trial that you must send to the other side and file with the court no more than 10 days after sending your Answer. You can also respond to a Complaint by filing a **"Motion to Dismiss,"** if you believe that the complaint is legally invalid or legally insufficient. A Motion to Dismiss must be based on one of the legal deficiencies or reasons listed under **Mass. R. Civ. P. 12.** If you are filing a Motion to Dismiss, you must also comply with the filing procedures for "Civil Motions" described in the rules of the Court in which the complaint was filed, available at www.mass.gov.courts/case-legal-res/rules of court.

4. **Legal Assistance.** You may wish to get legal help from a lawyer. If you cannot get legal help, some basic information for people who represent themselves is available at www.mass.gov/courts/selfhelp.

5. **Required information on all filings:** The "civil docket number" appearing at the top of this notice is the case number assigned to this case and must appear on the front of your Answer or Motion to Dismiss. You should refer to yourself as the "Defendant."

Witness Hon. Heidi Brieger, Chief Justice on _____, 20___.

Michael A. Sullivan
Clerk-Magistrate

Note: The number assigned to the Complaint by the Clerk-Magistrate at the beginning of the lawsuit should be indicated on the summons before it is served on the Defendant.

PROOF OF SERVICE OF PROCESS

I hereby certify that on 3/10, 2022, I served a copy of this summons, together with a copy of the complaint in this action, on the defendant named in this summons, in the following manner (See Mass. R. Civ. P. 4(d)(1-5)):

IN HAND TO WENDELL WEBB, CLERK, THE LIMUS CENTER FOR THE PERFORMING ARTS, INC., 270 TREMONT ST., BOSTON, MA

Dated: 3/10, 2022 Signature: JOHN RYAN, ESQ.

N.B. TO PROCESS SERVER:

PLEASE ENTER THE DATE THAT YOU MADE SERVICE ON THE DEFENDANT IN THIS BOX - BOTH ON THE ORIGINAL SUMMONS AND ON THE COPY OF THE SUMMONS SERVED ON THE DEFENDANT.

3/10, 2022

2281CV00628 Bush, Michael vs. The Wang Center for the Performing Arts, Inc. Doing Business as Boch Center

- Case Type:
- Contract / Business Cases
- Case Status:
- Open
- File Date
- 01/31/2022
- DCM Track:
- F - Fast Track
- Initiating Action:
- Services, Labor and Materials
- Status Date:
- 01/31/2022
- Case Judge:
-
- Next Event:
-

All Information | Party | Tickler | Docket | Disposition

Party Information

Bush, Michael
- Plaintiff

Alias

Party Attorney
- Attorney
- Chambers, Jr., Esq., Richard Cullin
- Bar Code
- 651251
- Address
- Chambers Law Office
  220 Broadway Suite 404
  Lynnfield, MA 01940
- Phone Number
- (781)581-2031

More Party Information

The Wang Center for the Performing Arts, Inc.
- Defendant

Alias

Party Attorney

More Party Information

Ticklers

Tickler	Start Date	Due Date	Days Due	Completed Date
Service	01/31/2022	05/02/2022	91	
Answer	01/31/2022	05/31/2022	120	
Rule 12/19/20 Served By	01/31/2022	05/31/2022	120	
Rule 12/19/20 Filed By	01/31/2022	06/30/2022	150	
Rule 12/19/20 Heard By	01/31/2022	08/01/2022	182	
Rule 15 Served By	01/31/2022	05/31/2022	120	
Rule 15 Filed By	01/31/2022	06/30/2022	150	
Rule 15 Heard By	01/31/2022	08/01/2022	182	
Discovery	01/31/2022	11/28/2022	301	
Rule 56 Served By	01/31/2022	12/27/2022	330	
Rule 56 Filed By	01/31/2022	01/26/2023	360	

Tickler	Start Date	Due Date	Days Due	Completed Date
Final Pre-Trial Conference	01/31/2022	05/26/2023	480	
Judgment	01/31/2022	01/31/2024	730	

Docket Information

Docket Date	Docket Text	File Ref Nbr.	Image Avail.
01/31/2022	Attorney appearance On this date Richard Cullin Chambers, Jr., Esq. added for Plaintiff Michael Bush		
01/31/2022	Case assigned to: DCM Track F - Fast Track was added on 01/31/2022		
01/31/2022	Original civil complaint filed.	1	Image
01/31/2022	Civil action cover sheet filed.	2	Image
01/31/2022	Demand for jury trial entered.		
02/24/2022	Plaintiff Michael Bush's Assented to Notice of withdrawal of plaintiff's counsel Richard Chambers.	3	Image
03/02/2022	Endorsement on Notice of withdrawal of Richard C. Chambers, Jr., Esq., as counsel for plaintiff (#3.0): DENIED without prejudice, must comply with Rule 9A Judge: Doolin, Hon. Michael		Image
03/21/2022	Service Returned for Defendant The Wang Center for the Performing Arts, Inc. Doing Business as Boch Center: Service made in hand; 3/10/22	4	Image

Case Disposition

Disposition	Date	Case Judge
Pending		